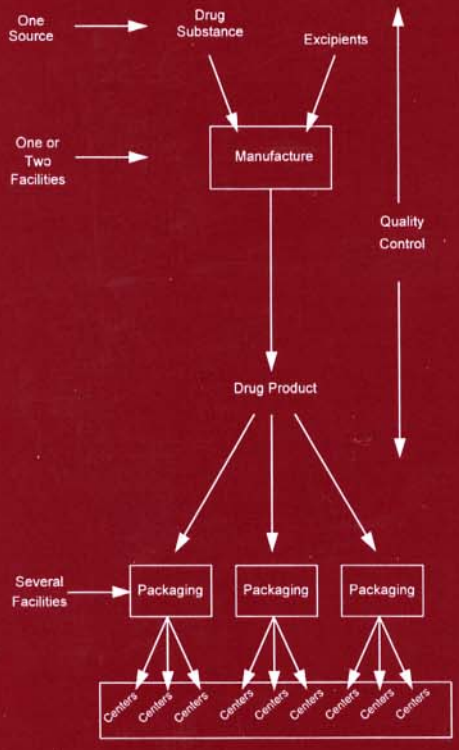
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 87

Drug Products for Clinical Trials

An International Guide to Formulation • Production • Quality Control



edited by
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Drug Products for Clinical Trials

DRUGS AND THE PHARMACEUTICAL SCIENCES

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Preface

Our objective in assembling this book was to call attention to a core competency in the arena of pharmaceutical development. We wanted to highlight the fact that the area of clinical trials materials was fundamental to any company's operations and that quite frequently the ability to produce and control such materials quickly and efficiently could lead to a competitive advantage. We were particularly attuned to this because of the checkered history of the discipline, and, since the whole industry has been undergoing massive restructuring, we felt it important to raise consciousness as to some of the issues and procedures that would allow the practitioner to flourish in an ever-changing environment. Accordingly, this book should not be regarded as a "how-to" book, nor is it to be regarded as overly comprehensive. Rather, we selected topics that addressed contemporary issues which would inform the reader about the concerns that the clinical trials manager faced in performing his/her tasks, and which would highlight some of the newer technologies that affected the way in which clinical trial materials are produced.

In the first half of the 1990s, pharmaceutical companies consolidated and reduced headcount in reaction to the converging pressures of thinning product pipelines, the increasing presence of generics, and budding managed care market power. Although these pressures have not yet dissipated, the consolidation of the industry will continue; companies are beginning to shift their focus to long-term growth opportunities and strategic positioning. Accordingly, as

editors, we identified topics that we thought were most significant for growth in the clinical supplies area, and that would help identify the best strategies and tactics that the practitioner could employ to achieve continued success and growth. Therefore, topics such as how to write SOPs and CANDAs, how best to deal with the FDA, the role of an IRB, labeling and legal aspects, patient/subject/investigator compliance, and safety monitoring have not been included, because this information is available in other medical publications, and we wanted to ensure that our contribution was a valuable addition to the armamentarium of those practicing in the field.

Several major themes related to current and future growth opportunities, and the challenges that pharmaceutical organizations face in achieving growth in the tumultuous healthcare market, are addressed in this book. These include:

- *Pharmaceutical firms' strategies must include product innovation, in both pharmaceuticals and biotechnology, rather than merely focus on winning price wars.*

  The chapter by Andrew J. Gorman and David Bergstrom addresses how innovation is encouraged in the discovery process, and the chapter by Vasken Paragamian discusses how innovation is so important in discovering cost-effective synthetic processes in scaling-up methods for producing large quantities of a new drug entity. John M. Baldoni and Choon K. Oh provide special insight into how innovation in the preclinical arena can enhance decision making as to the best chemical candidate with which to conduct clinical trials. New ways of treating stability data are introduced by Jens T. Carstensen in his usual inimitable fashion. As emphasized in Chapter 1, the clinical trials materials manager must stay abreast of new technologies to maintain effectiveness and grow professionally.

- *Companies can expect to form domestic and international alliances with other pharmaceutical and biotechnology firms in the next five years.*

  The chapter by Christopher J. Potter and the one authored by Peter J. Baines, Susan A. Charman, Gillian M. Clarke, Robin S. Roman, and Susan M. Walters both concern cross-functional areas affecting how clinical trials materials are handled in a transnational environment. Both address the different rules and regulations in Europe, and the latter addresses circumstances unique to Australia and Japan.

- *Companies anticipate outsourcing many functions that had once been considered necessary core competencies of classic fully integrated pharmaceutical firms. Such decisions are influenced by strategic focus, resource allocations, competitive market factors, and costs. Some of the larger*

fully integrated drug firms will spend millions of dollars in upgrading their own facilities, whereas the small biotech firms will elect to preserve their precious capital and outsource the production and control of clinical supplies materials.

To consider outsourcing, we commissioned an excellent chapter from Maureen E. Spataro and Michael G. Dragoon, who are intimately involved with this area from a provider and receiver's perspective on a day-to-day basis. In addition, this chapter raises the importance of accurate cost accounting. On the other hand, John E. Vogan and Jean Corriveau address the difficult area of handling toxic substances, which in reality is impractical to outsource.

- *Some companies rank information systems and corporate culture as the most significant challenges to internally developing and maintaining a competitive edge in their core competencies. Human resources are also regarded as very challenging. We believe that this concern reflects the difficulty in attracting and retaining people who are able to provide the knowledge and leadership required in the increasingly sophisticated areas throughout the organization that rely on the timely provision of clinical trials materials of high quality.*

  In Chapter 1, we introduce the concept of emotional intelligence and its utility in selecting staff to fulfill the critical role of a clinical trials materials manager. Nicholas P. Barker in his chapter on Total Quality Management speaks to the intricacies of how quality is measured in a clinical supplies department and provides food for thought regarding continuous improvement in people skills.

- *There will be an increasing awareness in the importance of information systems and data management in the next few years. This will lead to a burgeoning demand for just-in-time manufacturing, better communication systems, accurate cost reporting, and contract data in the industry.*

  In its totality, the book is really about how different groups best communicate with one another. The seminal work by Cary Blume stresses the importance of frequent and honest communication between the medical department and the clinical supply department. This concept is reinforced in the chapters by Graham J. Frank and by Thomas L. Jeatran and James Clark. The excellent chapter by Dorothy M. Dolfini and Frank J. Tiano highlights how crucial communication is in designing packaging systems for clinical trials supplies. Jeffrey D. Kosterich touches on how computers can make the difficult task of data tracking so much

easier. Chapter 1 introduces the future utility of artificial intelligence and rapid prototyping to the clinical trial formulations arena, and Gary W. Goodson and William C. Stagner expertly consider the critical aspects affecting clinical supply manufacturing.

- *The constantly evolving and easing of regulatory approval processes and harmonization of practices will impact the clinical trials arena in a significant and positive way. They have the opportunity to boost R & D efforts by adding time at the front end of the product life cycle.*

  Here we have chosen to address these issues in a multitude of works, viz., the previously cited multinational chapter by Peter Baines and colleagues; the concept of a time-based company is introduced in Chapter 1; Christopher J. Potter puts the concept of analytical validation in a unique perspective; and Gary W. Goodson and William C. Stagner address various GMP considerations affecting manufacturing. Bioequivalency considerations from a regulatory perspective are also discussed by C. T. Rhodes in Chapter 4.

In conclusion, we believe that the topics we have selected to form the basis of this book provide resonance to the stated purpose of discussing issues germane to the executive and practitioner alike regarding the important discipline of producing and controlling clinical trials materials.

Donald C. Monkhouse
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The Importance of the Role of the Clinical Trials Materials Manager

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I. INTRODUCTION

The emergence of the clinical trials manager as a truly important linchpin in the drug development team has not occurred by accident. Rather, it has been the culmination of three decades of struggle to gain recognition. It was not that the individuals involved did not have the requisite skill-set to achieve their rightful place, but the tools necessary to do the job correctly with aplomb were simply missing. With the advent of modern computer technology and proper training for the role, the clinical trials practitioner is now superbly positioned to assume his/her rightful role in the hierarchy of key players in modern drug development.

In selected pharmaceutical companies, the development, production, evaluation, supply, and control of clinical trials materials are ill-coordinated because team members have little idea of their exact responsibilities. Such lack of clear organizational structure can lead to poor quality and waste of money; for example, clinical trials materials may be grossly overstocked at one site, and yet be in desperately short supply at another. It is surprising how many companies have no idea of the cost of the development, supply, and evaluation of clinical trials materials. Lack of data on costs is obviously an impediment to efficiency. Although it is not always easy to assign costs, and it may well be that the budget developed may be relative rather than absolute, these estimates are still useful for monitoring trends and the quantification of costs for any project.

It is increasingly likely that budgetary data for clinical trials materials will be needed for a company to justify to the Internal Revenue Service (IRS) that its claims for tax credits for "qualified research" are justified. Since these tax credits can sometimes exceed several hundred million dollars a year, this issue is obviously of great importance. In the past, many pharmaceutical companies have claimed all expenses required for a New Drug Application (NDA) as meeting IRS requirements for "qualified research". However, there is reason to believe that the Agency is likely, in the future, to regard such an approach with a somewhat jaundiced eye. It is likely that the IRS will increasingly require more rigorous accounting to justify these tax credits. Since in many pharmaceutical companies, personnel working on clinical trials materials (probably acceptable to IRS as qualified research) may also spend part of their time on production trouble shooting, scale-up, or quality control of marketed products (probably not qualified research), more comprehensive budgetary data will be needed (1).

Examination of Form 483s (Notice of Adverse Findings) suggests that FDA investigators are currently not giving clinical trials formulations production and control a major priority in terms of current good manufacturing practices (cGMP) inspections. This situation, however, could easily change dramatically, and we could suddenly find that it would be "fashionable" for Food and Drug Administration (FDA) investigators to pursue all aspects of clinical trials materials with exceptional diligence. If so, some companies might well be the unfortunate recipients of a plethora of 483s, endangering both past and present NDA submissions.

There is an overwhelmingly strong case for cGMP training for all personnel working on clinical trials materials, with *specific* focus on problems peculiar to clinical trials products.

The increasingly international nature of the pharmaceutical industry affects virtually all aspects of research, development, production, and evaluation of drug products. Takeovers and mergers, such as occurred in 1995 resulting in the formation of Glaxo-Wellcome and Hoechst-Marion-Roussel, are making it increasingly appropriate to refer to major pharmaceutical companies as being

international or supranational in nature. Such megasized pharmaceutical companies, with operations in many parts of the world, can obviously see advantages in locating the development and production of clinical trials materials in a small number of sites. In addition, such companies have a special interest in globalization of standards for pharmaceuticals. This is one of the factors that has strongly stimulated "harmonization."

When we refer to international harmonization within the pharmaceutical industry, many of us think primarily of International Conference on Harmonization (ICH). However, there are other bilateral and multilateral modalities by which increasing standardization is slowly being effected, including the work of pharmacopoeias [US Pharmacopeia (USP), National Formulary (NF), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP), and European Pharmacopoeia (EP)] to standardize monographs.

Currently, the area of ICH activity that impinges most directly on clinical trials materials is the Stability Guideline. This document is significantly different from the 1987 FDA Guidelines. Most important, perhaps, the ICH places more emphasis on *principles*, whereas the 1987 FDA Guidelines gave considerable attention to specifics. The climate zone concept that has developed in Europe (2) is now gaining international acceptance. Retained product storage conditions are defined by ICH as 25 ± 2°C and 60 ± 5% relative humidity (RH); pharmaceutical products must normally be stable for at least 1 year under these conditions. Also, products should normally remain stable when stress tested at 40 ± 2°C, 75 ± 5% RH for at least 6 months. However, if these stress conditions are excessive for some products, a "fall-back" test of 30 ± 2°C and 60 ± 5% RH for 1 year can be used (3).

Examination of projects presently in the ICH pipeline does not indicate that there is likely to be any further policy with specific reference to clinical trials materials in the near future (4).

II. SPEED OF DELIVERY

The commercial benefits of high-speed development are well understood. Faster development can provide a longer effective life of market exclusivity for the approved product. It can also enable realization of a competitive advantage by allowing for launch before a competitor product can enter and gain a foothold in the marketplace. For a product that is licensed from another company, faster development can result in fewer penalties (or actual bonuses) to the licensee for any incurred delays. In a more subtle vein, faster development can prevent costly changes in the development plan, which inevitably occur when programs are unwittingly protracted and lack direction. Not surprisingly, if drugs are developed faster, their net present value (NPV) is enhanced just because fewer resources have been applied to the expensive and time-consuming preclinical and clinical phases of drug development (5).

The clinical supplies practitioner is superbly positioned to make substantial contributions to the project team by being able to make meaningful suggestions for optimization of timelines. This individual will be seen as a team player, and it will ensure recognition of the proper professional respect for active participation, and colleagues will seek early consultation on future projects. The worst image that can be projected is that nothing can or will be done to speed up preparation and delivery of supplies because of regulatory-imposed paperwork. Everyone should recognize that moving faster and finding better ways of doing things are essential to keep the company productive and competitive.

The clinical supplies practitioner, like other professionals, can contribute to keeping a watchful eye on fast-track programs to ensure that they do not get off-track or side-tracked. Because s/he serves so many masters and is part of so many project teams, there is a unique opportunity for the professional to judge if any particular program is out of sync with other programs or with itself. For instance, if one program clinician requests a year's supply of dosage forms before the Internal Review Board (IRB) has approved the protocol, or before the requisite regulatory documentation has been filed, the timing of delivery can be safely delayed in favor of another ongoing clinical program that is ahead of enrollment schedule, and is running the danger of depleting supplies. Likewise, issues that affect the Chemistry, Manufacturing and Control (CMC) section of the Investigational New Drug (IND)/NDA can be brought to the attention of the Project Management, e.g., the appearance of a new degradation product in a long-term stability program, the fact that a change in manufacturing process has been necessitated by a change in particle size distribution of the raw material, or that the formulation has been modified due to a slowing down of dissolution rate upon aging. Many such changes can have profound effect on the timing of an NDA submission, and any change in overall project direction must be carefully assessed by all the disciplines of the project team, including the clinical supplies practitioner. This places such issues squarely in the eye of the storm. It is important that the professional be able to handle the emotional stresses calmly and that the accusatory quips by misinformed team members be deflected unemotionally.

Where in the clinical supplies chain can the process be sped up? This chapter offers some answers.

A. Organizational Structure

In the modern era, *speed of development* has become the catchphrase that companies have used to benchmark their competitiveness. One of the favorite techniques of management consultants is reengineering, whereby various so-called rate-limiting functions have been restructured. One of the favorite target areas for this exercise has been the pharmaceutical research and development (R&D) function, and a subservient group within that group has been the clinical sup-

plies area. Another driver for reorganization has been the increasing regulatory surveillance of the way in which clinical supplies have been manufactured, analytically released, packaged, and shipped. Thus, various management solutions have been imposed on the discipline. As a result, two trends have emerged: the creation of small dedicated teams and globalized centralization.

One of the key areas of focus has been the positioning of the quality control (QC) unit within pharmaceutical R&D. Examination of the Federal Register Code of Federal Regulations (CFR) Title 21 reveals that there is a need for a QC unit, particularly for approving batches of drug product intended for commercial distribution. Also, there is reference to the need to properly review production and analytical records. In this way, FDA lawyers have clearly distinguished between testing and auditing and have demanded that there be two separate functions, with one having oversight of the other. With regard to drug products that are not for sale, but are for investigational use only, however, the law is much vaguer, since there is not specific provision for such a category within the CFR. Furthermore, the "Guideline on the Preparation of Investigational New Drug Products" (6), makes no reference to the requirements for a QC unit within or outside of pharmaceutical R&D.

It should be pointed out that the *c* in the term *cGMP* poses a dilemma for ethical pharmaceutical companies. The *c* implies that regulations are constantly changing and that unless close attention is paid to remarks made by FDA personnel during conferences or published in scientific/trade journal articles (sometimes referred to as *podium policy*), the company will not be in compliance. In quite a few cases, reference has been made to the fact that the FDA interprets clinical supplies as being covered by the CFR. Since these references have been regarded as interpretation and not strictly the law, pharmaceutical companies have adopted a variable posture when it comes to complying with the CFR. In a recent survey (7), this variability has been manifested by the management structure of the clinical supplies group within pharmaceutical R&D. All the companies surveyed maintained that they were in compliance because they had not been issued Form 483s. The following paragraphs outline the various types of management structures.

Depending on the culture of the corporation, whether time-based or quality assurance-based, the organization can be adapted to meet its own internal performance standards. For time-based competitors, speed and flexibility become the key drivers. Accordingly, traditional organizational structures have been reengineered to eliminate the barriers that have often existed between so-called functional departments. In the conventional organizational structure, various departments were staffed and equipped to achieve excellence in their own right. However, these "gold-plated" monoliths rarely communicated with their counterparts and were often in competition. As a result, coordination of tasks and the concept of being on a team were foreign, resulting in an ineffi-

cient mechanism for getting supplies out the door. The recent emergence of dedicated teams led by professional project managers to drive projects through to completion reflects a trend toward speeding up the process. By eliminating departmental barriers, however, there is a risk of reduced oversight, reduced compliance with standing operating procedures (SOPs), and increased faulty decision making–particularly when upper management exerts pressures to meet tight deadlines. Accordingly, two extremes exist in the various organizational structures, and a balance is struck between the business and compliance perspectives. The position of the fulcrum depends on the culture of the organization. For the business oriented structure, speed takes precedence at the expense of checks and balances; for the compliance oriented structure, attention to quality assumes priority over expediency.

At one extreme, dedicated project teams have been set up to work exclusively on a single project. Frequently, the team leader is a professional project manager, and each of the team members reports directly to this team leader, not to the traditional functional head of department. In fact, salary increases and performance measures are left entirely to the team leader, presumably to gain the subordinate's undivided attention. On the other hand, the titular head of department monitors the performance of the team member in carrying out laboratory duties. Teams are composed of members who come from various disciplines including the following: GMP manufacturing, analytical testing, methods development, stability, compliance, release, formulation development, and regulatory affairs. In such a dedicated situation, any conflict in priorities is eliminated; it is assumed that self-auditing will be sufficient to achieve the desired level of compliance. Not uncommonly, however, speed of delivery is the only measure for success and compliance is compromised. Furthermore, the lack of structure, training, and disciplinary oversight can eventually lead to a decay in the fabric and competence of the organization as a whole. The functional head is often reduced to the position of an observer, rather than that of a key player, and is generally viewed as a dinosaur of the conventional big Pharma.

At the other end of the spectrum, speed of delivery is sacrificed for maximizing independence in QA matters. In this model, departments of formulation development and analytical development report usually to a VP of Preclinical. Clinical supplies are manufactured within production, and their testing and release are performed by the QC group, reporting to the VP of Production. Quality Assurance is conducted by an independent department reporting directly to the president of the company. In this way, there is a clear separation of "church and state." This highly constrained but traditional approach allows for the strictest adherence to cGMPs (as applied to commercial products), but the varying nature of methods and processes encountered within R&D during the development scheme required for new products frequently demands more flex-

ibility than this scheme can provide. Those practicing this model defend their choice on the basis that technical transfer to production becomes a seamless process, while higher standards are maintained throughout. Here, functional heads are truly in charge of their subordinates, in both discipline matters and product team matters, and communication with so-called project leaders becomes a variable event, depending on the personalities involved. Because project team leaders have little influence over team member performance and salary increases, they have very little impact on the success of their projects. This often leads to creative tension between project management and departmental management.

Other structural models fall in between those cited earlier and vary based primarily on the geography of the QA/Compliance group. Some companies have it reporting to analytical R&D. These "old school" companies have so far failed to recognize the wisdom of avoiding conflict of interest issues through the creation of a separate compliance group within R&D. Other slightly more sophisticated companies have formed a subgroup of analytical R&D to make independent decisions regarding sanctity of data. A further improvement on this concept has been made by those companies who have separated the compliance function from both analytical and formulation and have made the VP of preclinical the arbiter of disputes, and hence, fully accountable. A good compromise for a high degree of independent compliance and acceptable speed of delivery has been achieved by making the compliance function directly accountable to a senior R&D executive, usually the president, and at least outside line management in development. Here, the analytical testing is conducted by analytical R&D, and the test results reviewed and product formally released by an independent compliance group.

The attractiveness of having the analytical testing group reside adjacent to the group responsible for manufacturing and packaging clinical supplies is of significant potential for increasing speed. This can be accomplished by reducing barriers between groups, particularly those of a geographic, communication, and cultural nature. Familiarity with the project's progress and nature of technical hurdles makes for a more efficient team and process. The compliance considerations are safeguarded in this model, since all the analytical data is reviewed by an independent compliance group, which also has the authority for formal release.

The advent of mega-mergers in which companies have sought to become more competitive worldwide, has provided an opportunity to increase efficiency and facilitate management of clinical studies. A direct beneficiary of this movement has been the role of the clinical supplies manager. In some forward-thinking companies, this role has been globalized. This has allowed the manufacture, release, and distribution of clinical supplies to be managed on a global basis. This concept, although not new, had been difficult to implement because

of the various parochial and provincial attitudes, particularly across the Atlantic and Pacific Oceans. However, the principal driver that has lowered the opposition has been the International Conference on Harmonization (ICH) process itself. Once the various governments agreed to harmonize practices among Europe, Japan and the United States, many of the seemingly irreconcilable differences were resolved. One of these differences was the way in which stability studies were conducted, and it is to the participants' credit that stability guidelines have now been harmonized, thus setting a precedent for other procedures (see previous discussion).

B. Proper Planning

Process management has revolutionized manufacturing. Companies around the world have reduced cycle times in their factories by studying each step in the manufacturing process and fluctuations in workloads for ways to reduce variation and eliminate bottlenecks. The clinical supply production process can be streamlined in much the same way (8).

Clinical supply practitioners must learn to think in terms of managing a "process". Most traditional companies, however, especially "big Pharma", think of clinical supply preparation simply as a list of projects rather than as a complex operation with a given capacity and workload. The universal reaction to such a process management approach is that the tasks are not nearly as repeatable in manufacturing, and standardizing the work would kill creativity. Each development project involves unique challenges that require unique solutions, but a lot of work in product development and in many other kinds of knowledge work is not unique. Many tasks and sequences of tasks are the same across projects. Process management exploits those similarities through standardization coupled with continuous improvement without destroying creativity.

The key principles in process management are as follows (8):

1. Projects are completed faster if the organization takes on fewer at a time.
2. Investments to relieve bottlenecks yield disproportionately large time-to-clinic benefits.
3. Eliminating unnecessary variation in workloads and work processes eliminates distractions and delays, thereby freeing the organization to focus on the creative parts of the assignment.

Process management is a particularly effective way to reduce the congestion that plagues almost all clinical supply operations when they undertake many projects at once and share staff and equipment across these projects. The typical project management approach is to create cross-functional concurrent multidisciplinary teams (formulators, analytical chemists, manufacturing, and packaging scientists) to identify and solve problems rapidly and early (see previous

discussion). Typically, these teams take on too many projects at once, thus leading to excessive delays. The most recent "popular" fix adopted by those companies who are losing the race in the development game is to create autonomous disciplinary project teams, each of which works on only one project at a time and presumably has all the resources it requires. This approach is expensive because it means duplicating rather than sharing resources. In addition, congestion can still arise within such projects, especially if the staffing plan underestimates the amount of rework that the team must perform. The rework inevitably results because these companies lose institutional memory, workers are no longer accountable to disciplinary experts, and virtually no mentoring occurs. Hence, many mistakes are made because of the "learning on the job" phenomenon, the lack of experienced oversight, and the peer pressure to take ill-advised shortcuts.

Successful companies do not allow their clinical supplies delivery to become rate limiting. They accomplish this by applying the following principles:

1. They spend a lot of time in the planning process, both with their customer base and within their group. Furthermore, they try to operate on a "pull" system, rather than on the traditional "push" alternative. In this way, through a rigorous review process for each new project, they attempt to start a new project only when another project is completed and out the door, thus making available the requisite resources to properly handle the newly arrived project. In other words, a balance between resources and workload is maintained, thus alleviating many stresses in the organization.
2. They adopt a vigorous cross-training program for their workers. Through this ongoing educational process, these companies invest in a truly flexible and efficient workforce.
3. They extend the concept of a regulatory-mandated SOP system to that of a "best practices" operation. These templates for how to perform a task are set forth for those procedures that are repetitive and rate-limiting. In stark contrast to those companies that have adopted the autonomous independent approach and that attack each new project differently, these "process" companies know the drill and avoid "rediscovering the wheel," thus making fewer errors and encountering fewer false starts. The avant-garde companies that have consciously elected to view the template idea as unnecessarily rigid bureaucracy and a recipe for alienation and regimentation are now paying the price of a lost infrastructure and the increased out-of-pocket expenditures due to excessive outsourcing. Of course, the cross-functional training program offers the opportunity and ensures that the best practices are inculcated into everyday habits. These practices constantly undergo improvement as the training program evolves and matures.

C. Use of Modern Computer Technology

Information systems are vital in providing accurate, timely, statistical data to management. The new excellence, however, requires information on a continuous basis—real time. This control of information, service to patients, and money must be monitored and controlled continuously. Management must improve performance for the people who work within these processes. Errors and inaccuracies are frequently the most significant contributors to poor compliance and less than total effort by subscribers.

Obtaining and assimilating information into clear controlled courses of action require skilled management backed by sophisticated but user-friendly systems. One such technology comes out of the voice response industry and is termed *computer telephony* systems. Here, advanced central randomization brings many benefits to clinical trials by providing 24-hour randomization and easy access for investigators by touchtone telephone. Telefacsimile is used to confirm enrollment. A variety of automated reports is available to get enrollment information quickly to clinical teams. By using such a system (9), the clinical supplies manager has a minute-by-minute record of enrollment at any particular site and across all clinical sites. This information is particularly useful when there is a shortage in drug supply or the drug is chemically unstable and has to be kept in the refrigerator at home base. In the latter case, drugs can be shipped when needed to the site where they are needed by overnight express mail. In the former case, the valuable supplies can be inventoried at home base and metered out "just in time" (JIT) to the clinical sites that are consuming the most drug. By knowing the date of administration of first dose, which patients get the active drug and which get placebo, and when the patients need to visit the clinic for a resupply, it allows the clinical supplies manager to accurately predict consumption rate. In this way, it is possible to avoid shipping a drug that languishes on the shelf at a lackluster site, and when supplies are predicted to be running low, they can be remanufactured in a timely and cost-effective manner.

Globalization could never have been contemplated in the clinical supplies area if the new technologies had not been at the clinical supplies manager's disposal. Such technologies have given the clinical supplies manager better control of the status of supplies out in the field and in the warehouse.

D. New Methodologies in Drug Discovery and Development

1. Combinatorial Chemistry

Modern drug discovery efforts are exploiting at least three core technologies aimed at increasing the efficiency of finding drug leads: genomics, high-throughput screening, and combinatorial chemistry. Research aimed at the

human genome is rapidly multiplying the number of disease targets. Screening methods using biological assays can quickly show if a compound is a "hit"; that is, if it has activity against a target. Combinatorial chemistry methods can produce and help optimize the compounds used in screening. Many pharmaceutical companies view this hot area as technology they *must* have to compete.

In the past, most drugs were discovered by screening collections of compounds to find a random hit. Companies with larger collections or libraries have had an empirical advantage. Although more compounds can be better, especially with the advent of high-throughput robotic screening, an expanding knowledge of the molecular biology of disease is shaping the design of these libraries.

Speed—which translates into time, money, and an ability to compete—is a key concern in drug discovery. Laborious synthesis methods in which a chemist makes one compound at a time cannot keep up with the desired pace. Combinatorial chemistry, broadly defined as the generation of numerous organic compounds through rapid simultaneous, parallel or automated synthesis, is changing the way in which chemists create chemical libraries and is expected to change the speed at which drugs are found. After finding a lead from a large combinatorial library, one can apply this chemistry to patent protection by creating thousands of compounds around an active structure and making it difficult for competition to break through.

Analytical control over the chemistry and in identifying compounds is as, or more, important in making millions of compounds. Especially important is the ability to match shape and chirality of targeted enzymes or receptors using stereoselective methods. A very useful tool is liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), which allows accurate identification and quantitation of very small amounts of compound. Here the MS fragmentation pattern can provide considerable insight into structure of the compound under investigation, and complement other structural investigatory tools such as nuclear magnetic resonance (NMR) spectrometry and x-ray diffraction. Companies that use a Laboratory Information Management System (LIMS) (10) have better control over the acquisition, flow, and management of data.

2. *In Vitro Cell Culture Testing Modalities*

With all these new leads coming to the fore, there is mounting pressure to ensure the safety of these substances. While the animal rights movement has focused public attention on the use of animals in toxicological and safety testing, shifting the debate to the public forum has fostered a number of misconceptions. For instance, current in vivo methodologies require the study of complex interactions of tissues and organs, events that can occur only in a living animal. Therefore, until the recent development of culturing cells ex vivo, researchers did not have many alternatives to the use of whole live animals in

toxicology and safety testing. In vitro tests for products are now becoming available that can replace the need for live animals. These include artificially grown skin systems that can be used for skin and ocular irritation, phototoxicity, corrosiveness, and sun sensitivity. (The Draize ocular and skin irritation tests alone account for over $600 million annually worldwide.) Additionally, the ability to culture enzymatically active animal and human liver cells (hepatocytes) in long-term cultures and grown in a three-dimensional, anatomically engineered fashion offers the opportunity to examine drug candidates for their proclivity to be metabolized by the liver without the use of animals. Using human cells avoids the leap of faith required to assume relevance for humans from animal studies. The idea is to expand liver parenchymal (functional) cells in co-culture with stromal cells and getting them to adhere and grow onto three-dimensional frameworks, which allow cells to adhere and assemble into tissues that more closely resemble their natural counterparts in the body. Once the biodegradable polymer scaffolds erode and disappear, a construct is left behind that resembles all the major types of cells normally found in the liver, the cells producing growth factors that promote the development of organ cells into functioning tissues. These constructs can presumably be easily reproduced in large quantity and can be used in drug screening because they function like a normal liver. Such in vitro flow-through systems can be used to efficiently differentiate those compounds that would suffer from a high first-pass effect. Other humanoid-like organs such as the pancreas and kidney are also under development (11).

3. Physical Methods

With the onslaught of these new methodologies, the bottleneck in drug development is no longer the lack of new leads, but the lack of availability of formulated dosage form supplies to test in the clinic.

As discussed in Chapter 2, several limiting factors preclude a drug's suitability for clinical trials. These include absorption, metabolism, solubility, and stability. Absorption can be screened using $CaCO_2$ cells. Metabolism will soon be able to be screened by the techniques already discussed in this Chapter. Stability is another area that is receiving new attention through the adaptation of microcalorimetry.

Isothermal microcalorimetry is used to measure heat output of unstable systems at or just slightly above room temperature. By comparing the heat generated by a number of compounds in a series, it is possible to cull out the most unstable ones, and, by experience, predict if such compounds are suitable for commercialization. In a similar fashion, drug-excipient mixtures and even dosage forms can also be screened and the most stable one chosen for clinical trials. Such experiments usually can be performed in less than a week and rapid decision making can minimize development time.

4. The New Paradigm

In traditional pharmaceutics, the practitioner usually obtained/earned job security by being able to accurately and precisely determine the physicochemical attributes of a candidate drug. If the molecule was unstable, insoluble, poorly absorbed, or highly metabolized, the physical pharmacist applied expert training either by stabilizing the compound by adding excipients or adjusting certain parameters, or by increasing solubility by reducing particle size or changing salt form; or by increasing absorption by adding wetting agents or by increasing dissolution rate by a prescribed cadre of "tricks"; and by reducing metabolism by adjusting biopharmaceutical parameters such as input rate or site of absorption. Months/years of valuable elapsed time were often consumed by such an exercise, often to no avail. In the new paradigm, where speed is of the essence, such acts of futility management will no longer be tolerated. In the future, this act of "retrofitting" lead candidates will become a *modus operandi* of last resort and will be taught in pharmacy schools only for the sake of principle and example. Rather, because the discovery chemist will have a plethora of compounds from which to choose as a result of the combinatorial screen, if a compound is shown to be deficient in one of the four critical properties, it will simply be replaced by another with improved properties, but with similar or slightly reduced potency.

5. Outsourcing

What can the clinical supplies manager do to ensure that productivity and throughput of clinical supplies meet management's expectations? One option is to "outsource". Chapter 13 discusses this alternative in detail. Essentially, pharmaceutical companies prefer to reserve their own resources for their most promising candidates and to send out the manufacturing and packaging of the rest. The current trend is to use those contractors who are vertically integrated; that is, they can formulate, manufacture, package, and release clinical supplies under one roof. This eliminates costly delays caused by technology transfer; minimizes time spent identifying and coordinating multiple vendors that each have a specialty area; provides continuity of data integrity, data transfer, and archiving; simplifies audits and site visits, and reduces costs through prepackaged services and economies of scale within the provider.

6. New Manufacturing Technologies

An emerging second option is to take advantage of a new methodology termed *desktop manufacturing* (or rapid prototyping or three-dimensional printing). The principle by which these processes work is that a formulator designs a dosage form on a computer workstation using computer aided design software (CAD). The workstation prints the information to a mechanism that translates the CAD

files into solid three-dimensional objects, generally by building the object layer by layer.

Three-dimensional printing (12) allows a high degree of design flexibility, not only in terms of macro/microarchitecture, but most important, in composition and surface texture within the part being manufactured. The process is easily scaleable, permitting quantities ranging from preproduction through manufacturing volumes to be made using a single process. These factors distinguish this unique process from other fabrication approaches and make it ideally suited for manufacturing clinical supplies where materials and design play critical roles in product differentiation (matching placebos), where shortened product lead times are of critical strategic advantage, where traditionally large quantities of valuable GMP material are severely limited, and where product/process validation underlies the ability to gain product marketing approval to ensure patient safety. The process delivers drugs through a printhead into a bed of powdered excipient blend, and the particles are "glued" together into three-dimensional (tablet or capsule) shapes using suitable polymers or "binders." Thus, the prototypical dosage form produced for clinical supplies can be fabricated in production quantities *without changing the process*. This simplifies transition to manufacturing with faster, less costly scale-up and prescribed validation of production. Numerous production steps are also consolidated into one machine resulting in savings in plant design, capital costs, and space requirements. These features avoid the design-related compromises and reduce the cost and time normally associated with traditional processes. Thus, the need for a "bioequivalence" study can be completely avoided using such an approach. Additionally, toxic or potent compounds can be safely incorporated in an excipient "envelope," thereby minimizing worker exposure. Altering release rate or sequence of release of combination products is also easily accomplished through the use of suitable polymers. All of these adjustable parameters can be secured for future reference and guidance through the adoption and maintenance of an "expert system," where the use of artificial intelligence can speed up excipient and binder selection, as well as build strategies, including geometry, texture, shape, and binder addition rates.

E. Emotional Intelligence

A successful manager of clinical supplies must not only have a high IQ, but also must have a high degree of social intelligence, i.e., the ability to interact with other people. In this case, however, "other people" includes the very demanding members of the medical research community. In an industrial environment, the so-called bedside manner of the clinician is often forgotten when supplies for the clinic cannot be obtained, even if the original requested timetable was admittedly unrealistic. In such situations, it is easy to yield to the

emotion of the moment and lose focus. It takes quite a bit of self-discipline to overcome built-in emotional triggers (in the primitive state, humans needed quick reactions to survive the Savannah or forest). An undisciplined emotion can easily hijack one's personality when it falsely reads a situation as an emergency. In a modern business setting, some kinds of instinctive emotional responses are not only inappropriate, they can terminate a career.

The ability to manage one's feelings well is a central factor in achieving success, whether in business or politics, and in particular in the clinical supplies arena. "Since the time of Plato, a sense of self-mastery, of being able to withstand the storms of everyday life, has been praised as a virtue. The Greeks called it *sophrosyne*, which meant care and intelligence in conducting one's life. This does not mean that one should be cold and calculating, as it is often interpreted in business. What is wanted, wrote Aristotle, is emotion appropriate to circumstance" (13).

In the past, pharmaceutical companies used to shunt failing scientists into the clinical supplies function. This is now recognized as a tremendous mistake. As a variation of the "Peter Principle," people were promoted to the level of their emotional incompetence. This dysfunction manifests itself in group negotiations, where negative thoughts expressed by an emotionally inept clinical supplies manager transmit throughout the group (and company), and the team environment never quite fully recovers. On the other hand, the positive, emotionally intelligent manager, who is self-aware and sensitive to the emotional makeup of others, is priceless. An emotionally effective clinical supplies manager can lead his or her team or customers toward a sought-after goal in the face of numerous setbacks, adversity, and failures. Astute companies are taking steps through appropriate training to transform the interpersonal skills of clinical supplies managers and reduce the domination of the corporate hierarchy by the classic tone-deaf manipulative jungle fighters celebrated in the business press no more than a decade ago. "Globalization and new information technologies have increased person-to-person commercial contacts across continents and between nations. This new competitive reality puts emotional intelligence at a premium in the workplace and in the marketplace" (13).

Thus high-performance clinical supply practitioners now spend most of their time interviewing customers—clinicians, chemists, nurses, or patients. They listen. More consultant then pitchman, they nimbly match the customer's needs to the appropriate aspect of the clinical supplies. This is in stark contrast to government agencies that are not accountable to their customers and that are notoriously insensitive to their clients' goals. There is no incentive to feel what the customer feels. Modern clinical supply practitioners recognize that the company's survival depends on a satisfactory emotional exchange between the company, the team, its members, and its customers. This vital provider-customer relationship is further discussed in Chapters 7 and 17. Smart companies

now use quantitative measures of emotional quotient (EQ) and intelligence quotient (IQ) to selectively hire personnel who can exhibit qualities and behaviors suitable for fulfilling the job description of such a pivotal position as the clinical supplies manager.

III. SUMMARY

The world surrounding the clinical trials materials manager is constantly changing. To survive and grow, the clinical trials materials manager needs to stay abreast of the developments in the discovery arena, as well as take care of the core business in development. This means exploiting new technologies that can maintain competitiveness and optimize speed of delivery.

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Drug Discovery Considerations

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I. OVERVIEW OF PRECLINICAL DRUG DISCOVERY

The major challenge of any drug discovery program is to bring together a cross section of talented, multidisciplinary scientists involved in evaluating and characterizing the pharmacological profile of a new drug entity. The basic principles involve defining the mechanism of action, potency, efficacy, safety, toxicology, and metabolism of the lead compound. Synthetic/medicinal chemistry determines the structural characteristics that may provide the desired biological activity. This may be based on a rational drug design approach and classical structure-biological activity relationships. However, recent computer technology advances

have provided for the molecular design approach based on the computational design of chemical entities, which may "fit" the active moiety of the target enzyme, membrane receptor site, or a clearly characterized gene sequence. Most commonly, the compounds are then evaluated by biochemists, cell biologists, pharmacologists, or biotechnologists using various in vitro screening assays (enzymes, membrane receptors, cellular organelles, or isolated tissue preparations) to determine the intrinsic activity of the drug candidate. This may involve membrane-based receptor binding assays or cloned receptors in primary cellular cultures, which are capable of screening a large number of candidates in a rapid and timely manner (high throughput screening. A compound demonstrating a certain predefined level of activity (IC-50, ED-50) can be considered a compound for further preclinical development work. The various "decision tree" criteria that define a candidate as a lead compound will be discussed in more detail later.

Once the in vitro assessment has identified "active leads," pharmacologists undertake in vivo testing of the drug candidate in appropriate animal models that best predicts the compound's ability to alter a particular disease target in humans. This establishes whether the drug candidate demonstrates the all-important biological activity. Pharmacologists study the compounds in various species establishing the dose-response characteristics for the selective drug candidate. In addition, pharmacologists establish the therapeutic index (ratio of side effects to the biologically active dose) by carrying out safety assessments in various species (cardiovascular side effects and overt effects). Bioanalytical chemists provide the expertise to explore the effect of the animal on the drug (metabolism), while toxicologists and pathologists explore the effect of the drug on the animal. The identification and characterization of potential metabolites that are produced by the parent compound through various metabolic routes are the goals of analytical chemistry.

During each of these preclinical, drug discovery stages, the clinical pharmacology group interacts with the preclinical scientists to remain continuously informed of the preclinical findings of the lead drug candidate so that effective integration of preclinical information can be established for determining first dose in Phase I clinical trials (human metabolism and drug tolerance studies). In this regard, the pharmaceutical development expert provides valuable information about the solubility, stability, and formulation properties of the compound. It is imperative, from a clinical and marketing standpoint, that the most optimal formulation be identified for early preclinical testing. The pharmaceutical development/formulation experts should be integrated very early into the preclinical development program. It is at this point that the preclinical pharmaceutics expert is able to reconcile the physical chemical profile of a lead candidate with drug transport experimental information generated using various in situ and in vitro methods to recommend dosing strategies that will maximize

bioavailability and therapeutic performance in vivo. Patent attorneys play an important role early in the discovery process in protecting the company's technological/research investment, as well as protecting the intellectual property throughout the development stages of the lead drug candidate.

The various stages and the multidisciplinary expertises involved in the preclinical drug research and development (R&D) process are discussed in more detail in the following sections. At this stage of the pharmaceutical development process, it is crucial that strategies and assays be established that provide the necessary support information for eventual submission and evaluation of the final product of preclinical efforts, that is, the Investigational New Drug application (IND). It is also important that this information be generated in a timely and competitive manner. This is a critical consideration for the preclinical scientist so that the patent life of the compound is not unreasonably affected at the time of market launch. The challenge of a company's drug R&D programs is to shorten the estimated 10 to 12 years of development from discovery to market launch. The scientific design and strategies of preclinical discovery programs in the pharmaceutical industry should not only be driven by a clear unmet clinical need, but also integrated into the assessment of the market potential of the drug candidate and the return-on-investment for developing the compound. This becomes even more crucial based on the estimated $260 to $320 million necessary to bring a lead candidate to market.

This chapter provides an overview of the various strategies, criteria, and basic issues that present a challenge to the preclinical assessment and development of a drug candidate. The roles and responsibilities of the various functional support experts are described in an integrated manner. The individual scientific disciplines will not be developed in exhausting detail, although the basic strategies and goals of each preclinical functional unit are certainly emphasized. It is hoped that this will serve as a basic framework for formulation experts to gain insight into preclinical drug discovery per se, and to identify areas where their input can have an impact. It is truly at this point where pharmaceutics is "value-added" in improving the percentage of research compounds successfully moving from discovery through development and on to commercial manufacturing.

II. DECISION CRITERIA AND STRATEGY

The *overall* strategy of a drug discovery program involves integration of chemical synthetic and biological criteria. In general, the scientists from the medicinal chemistry functional unit should identify lead candidates based on the following criteria: (1) it should be able to be synthesized with the fewest number of synthetic steps; (2) the synthetic steps should not involve complicated or difficult pathways and utilize a source substance; (3) the base substance should

be readily available and of low cost from the source; and (4) the synthetic process must lend itself to bulk, scale-up manufacturing. The analytical group is responsible for determining and verifying the structure and the purity of the lead candidate. The parent chemical entity must demonstrate a minimal level of potency, which is determined in a series of in vitro, high throughput assays. The potential candidate then must demonstrate biological activity via a desired route of administration (oral, intramuscular, subcutaneous, nasal percataneous, etc.).

Although a drug candidate may be readily absorbed, it must demonstrate a certain degree of effectiveness (potency) in inhibiting or activating a targeted biological mechanism and a reasonable duration of action. Once biological efficacy criteria have been fulfilled, the drug candidate must demonstrate a large separation between the efficacious dose and a dose that, produces adverse side effects. The ratio between the efficacy dose and the side effect dose is the *therapeutic index*. The minimum therapeutic index criteria needs to be established early in the drug discovery process, and based on the input of the clinical research staff which has experience in clinical trials and practice. Input from Drug Regulatory Affairs may be solicited to provide information of the guidelines or criteria established by the respective regulatory agency (e.g., Food and Drug Administration). This information is often incorporated into the decision criteria for drug discovery programs.

Validation of the intrinsic activity and biological activity of the compound is necessary before the more expensive and time-consuming toxicological, formulation, and metabolism studies are carried out. The toxicologist or pathologists play the important role of evaluating the safety of the new drug leads in animal models before administration to humans. The drug metabolism experts identify how the drug is absorbed, distributed among tissue and body fluids, and metabolized and excreted in various species. They determine the degree of binding to plasma proteins and an index of effective plasma concentrations (plasma half-life, $t_{1/2}$). Tremendous pharmaceutical and analytical development capacity has been consumed where insufficient validation of early preclinical indicators of activity have caused inappropriate or premature development false starts. To minimize this occurrence, the pharmaceutic scientists should actively assert themselves into these early research activities. Obviously, this requires the modern pharmaceutic scientist to have different personal skill sets than many predecessors. These include basic pharmaceutics training, but also the personality and people skills of negotiation, communication, and collaboration.

The establishment of decision criteria for a drug discovery program is more easily based on standard comparisons with drugs of the same or similar therapeutic indication, which have been previously studied and marketed and are currently being utilized in the treatment of the targeted indication. If there is no standard drug currently gaining experience in a disease population, the

decision criteria for potency and efficacy must be established by reliance on animal models of the human disease state. However, it is crucial that strict criteria for safety, toxicology, and pharmacokinetics be established with the safety and clinical maintenance of clinical trial volunteers kept in mind.

An example of a therapeutic project decision criterion is the discovery and development of compounds that antagonize or block dopaminergic and serotonergic receptors in the central nervous system for the symptomatic treatment of schizophrenia. Standard drug entities currently in clinical use are haloperidol and clozapine. Prognosis for improvement in the therapeutic treatment of schizophrenia is based on the fact that some patients show resistance to treatment of the primary ("positive") symptoms with haloperidol while also causing secondary ("negative") symptoms such as social withdrawal, hallucination, and dyskinesia. Haloperidol, thoroughly in the class of "typical" antipsychotic agents, shows greater affinity for dopamine-2 receptors in the brain. It was hypothesized that if simultaneous blockade of serotonin-2 receptors could also be achieved by a single chemical entity, improvement in the resistant population of patients and elimination of symptoms could be achieved. Thus, the "atypical" antipsychotic agent, clozapine, was developed. Clozapine is a potent, dual blocker of dopamine-2 and serotonin-2 membrane receptors in rat brain tissue and is clinically effective in treating both the positive and negative symptoms of schizophrenia. However, patients must be monitored for drug-related blood disorders, termed *agranulocytosis*, in addition precipitous reductions in blood pressure when the patient assumes an upright position. These two side effects present concerns for managed care costs, as well as a clinical concern for patient compliance in taking the medication and probability of reentry of the patient into a treatment institution. Therefore, a decision criterion for a potential drug lead for the symptomatic treatment of schizophrenia must show selectivibly and potency for binding to dopamine-2 and serotonin-2 receptors, which are equal to or, ideally, significantly greater than those for clozapine, but lack the serious side effects.

In vitro radioligand binding studies utilizing brain tissue, rich in dopamine and serotonin receptors, are carried out in the presence of the drug candidate to determine its affinity for binding to the targeted receptor. However, this in vitro assay does not determine whether the compound is indeed functioning as an antagonist of receptor-mediated neural activity. Several in vitro functional assays or, more classically, in vivo assays are carried out to determine the potency for the compound to block the functional effects of activating dopamine-2 and serotonin-2 receptors. One strategy is to test the effectiveness of the intraperitoneal injections of the compound to inhibit climbing behavior of mice induced by dopamine. The relative potency (ED-50) of the compound to block this behavior must be significantly greater than clozapine and haloperidol in order to be advanced to further in vivo testing. In addition, cardiovascular safety

assessment in various species such as rats, dogs, or pigs should show that the candidate does not elicit changes in blood pressure or heart rate at doses that are at least four times greater than the dose for demonstrating antipsychotic activity in in vivo animal models. Pharmacokinetic assessment should show that plasma levels are achieved with oral dosing that are equivalent to plasma levels achieved when administered intravenously or subcutaneously. This assessment must be done carefully. In many cases, subtle biopharmaceutic aspects make these comparisons difficult and result in erroneous product development plans being laid. Some of the biopharmaceutical considerations should include relating the physical-chemical properties of the compound such as solubility or degradation mechanism to the in vivo environment, as well as gastrointestinal motility, absorption windows and other drug transport phenomena (e.g., gut wall metabolism). This demonstrates that the candidate is well absorbed and not quickly metabolized upon first passing through the liver. Brain levels of the drug candidate should exceed plasma levels to indicate optimal penetration into the brain, the target organ. Effective plasma levels should remain elevated long enough to prevent multiple daily dosing of the compound but not so long that a prolonged time is required for the compound to be excreted if an untoward side effect occurs. Toxicological studies in various species should indicate lethal doses of the drug candidate that are significantly greater than the standard antipsychotic drugs previously tested and/or significantly greater than the doses which proved efficacious in the animal behavioral models.

There are no specific, quantitative criteria for the therapeutic index for safety and toxicological effects set by the Food and Drug Administration (FDA) or any other regulatory agency. This should be determined based on the indication and other factors considered by the project team of the company. However, it should be emphasized that all therapeutic drug candidates must demonstrate a clear risk-benefit criterion before they are considered for clinical development. In the preclinical arena, this is difficult to determine since there is uncertainty as to the relevance of the in vitro assays and animal models to the human condition. There is no sound predictor of how humans will metabolize or respond to a drug candidate relative to the animal models. This is the reason for testing in a wide range of animal species and disease models. It is assumed that humans will handle the drug in the body similar to the most sensitive animal model. However, this remains uncertain until the appropriate safety, drug tolerance, and efficacy trials are conducted in humans.

III. CHEMISTRY

Although the approaches to the discovery of a new drug candidate may be based on in-house synthesis of new chemical entities (molecular modeling), the development of compounds based on a previously defined structure-activity re-

lationship ("me-too" compounds) or based on the in-licensing of compounds synthesized by other companies or sources, the efforts of the medicinal chemists represent a critical starting point in the drug discovery program. The goal of the medicinal chemist is to design and synthesize novel chemical entities with unique, patentable structures and/or mechanism of action, which dfferentiate them from other marketed drugs. However, the role of various chemical scientists slightly differ in the time of their contribution as well as their goals and objectives. A new chemical entity (NCE) may be prepared by the synthetic, medicinal chemist based on the traditional approach of varying molecules by structural alterations or substitutions, the physical combination of different molecular structures with each structure possessing a defined activity to obtain a desired combined activity in one single molecule. The rapidly developing field of molecular modeling has come into prominence during the last decade. The use of computer-based molecular modeling provides the technology to design a small molecule or synthesize a biologically active fragment of a previously defined molecule and to determine or fit the necessary three-dimensional site that will activate or inhibit the biological site of interest. The target may be a membrane-based receptor site, an active enzyme site, a high-molecular-weight protein known to mediate a second messenger pathway of intracellular origin, or a targeted fragment of a gene responsible for highly specific cellular protein synthesis. The synthetic chemist then prepares the chemical compounds in quantities adequate to screen in subsequent biochemical or early biological assays.

Traditional efforts of "me-too" chemical synthesis are directed at mimicking some portion of an existing marketed compound by designing and synthesizing patentable analogs of a derivative of the known agent. However, other alternative sources can be utilized to acquire chemical synthetic candidates. The most exciting approach to rapidly identifying unique and novel chemical entities is the use of "combinatorial libraries." This consists of rapidly synthesizing small (micromolar) quantities of compound through the use of robotics and automated techniques. The goal is to synthesize and characterize hundreds of thousands of compounds a year. This provides access to a significant number of compounds that have been catalogued and structurally characterized. Storing these chemical entities could involve placement on a microchip or in 96-well microfilter plates for testing. The challenge for the future is to adapt high throughput testing systems that can screen the vast number of compounds available in these combinational libraries; as many as 5,000–10,000 compounds per day can be screened.

Compounds can be purchased from catalogued libraries of various chemical companies and used to test a structure-activity hypothesis in order to synthesize a more specific structural entity. The purchased compound is of no real value since it is not patentable as a composition of matter by the company

purchasing it. Limited potential as a source and proprietary for compounds are chemical entities discovered or under study from academic institutions or other companies made available through contact with the institutional technology liaison managers. However, the public disclosure and lack of novelty usually limit the value to an ethical pharmaceutical company.

The computational chemistry approach may be receiving more widespread attention in an attempt to mimic, by small molecular synthetic approaches, the selective activity of neuroendocrine proteins. Large proteins do not demonstrate acceptable absorption or penetration across epithelial membranes (so-called blood-brain barrier) due to their large molecular weight and insoluble chemical properties. Some companies have attempted to bypass these limitations by developing sophisticated drug delivery systems that would carry large protein molecules to the target site and "unload" the protein in order for it to exert its activity. The pharmaceutical development formulation staff is pivitol in this regard by developing or identifying technology that can enhance site-specific drug delivery. Protein drug delivery has literally added a new dimension to the technical challenge facing the formulation scientist. Maintenance of tertiary protein structure during the drug delivery process is truly at the leading edge of formulation science. This also forces demands on the analytical development scientist in characterizing and developing appropriate control parameters for these complicated molecules. This is a challenging and difficult approach since additional factors are introduced such as (a) confidence in the control of the amount of active compound delivered, (b) the slow or rapid rate of metabolism of the chemical entity leading to serious side effects, uncontrollable washout periods and difficulty in attaining efficacious levels, and (c) the inability to easily monitor levels of the compound in plasma or other body fluid. Each of these factors would impose a great burden on the pharmaceutical/clinical development team in demonstrating to the regulatory agency that the drug under study would be an efficacious approach that could be prescribed and administered, with little or no risk to the patient.

However, the computational approach to drug design does lend itself to determine more clearly the three-dimensional molecular site of interest that mediates biological activity, with the goal of designing the small molecule that will act as a more selective ligand or inhibitor (e.g., membrane bound receptor enzyme site).

Another potential source of new chemical entities is provided by plants or other natural products. This approach has imposed many *limitations* in the pharmaceutical industry and provides *limited* opportunities. The patentability of natural products or the isolated purified active constituent is always under question; with the high risk of patents being challenged and/or withdrawn by third parties. The chemical synthetic or other approaches have provided valuable candidates that can saturate the biological screens without the burden of col-

lecting and transporting plants and extracting the active ingredient. The uncertainty of continued availability of the species and seasonal variations imposes added concerns in this approach. Regulatory limitations pertaining to the collection, shipment, and export/import of such material also impose an added burden. An example of the difficulties surrounding such an approach is the developent of Taxol, the cancer-treatment agent derived from the bark of a tree. Environmental impact on the plant species, the relative ability of the active ingredient, and regulatory concerns were difficult obstacles to overcome from approval to commercialize.

The medicinal chemist continuously receives information from the pharmacologists regarding the biological activity and the safety/toxicological profile of various candidates that have already undergone screening. Based on this information, the modeling chemists can make alterations in structure to optimize or enhance the biological activity of the chemical series, or to reduce the side effects and to optimize drug delivery formulation. Thus, close communication is imperative between the chemists, biochemists/pharmacologists, and pharmaceutical development experts to optimize the structure-activity relationship of the targeted chemical entity. When this product development team has chosen the prodrug delivery approach, the pharmaceutical development scientist becomes key in planning and performing in vitro and in situ experiments assessing the ester hydrolysis rate and recommending appropriate dosing strategies (i.e., site). Once the chemical sources have been obtained based on the preceding approaches, the next steps in the drug discovery process are primary biochemical screening and secondary biological evaluation.

IV. BIOCHEMISTRY AND PHARMACOLOGY: PRIMARY SCREENING AND SECONDARY BIOLOGICAL EVALUATION

The approach of carrying out primary (biochemical) screening in an in vitro system is highly attractive since it permits large numbers of compounds in small quantities to be tested in a short time and at low cost. However, even the best in vitro systems cannot begin to mimic the physiological complexities inherent in the intact body. In vitro systems have become extremely useful while being adapted to so-called "high throughput" screening assays that rely on robotics and automation to screen as many as 100,000 crude compounds in a year that have undergone resin binding and radioactive tagging.

The choice of the initial in vitro system, of course, depends on the field of interest of the company and the pathophysiological understanding of the targeted disease. As mentioned earlier, a considerable amount of successful screening has been performed for years utilizing cells that contain functional receptors on plasma membranes or clearly defined enzymes in which scientists

search for compounds that act as agonists (receptor activators) or antagonists to the receptor or enzyme of interest. The most common approach to screening for a compound's agonist or antagonist activity with purified receptors is to "label" the compound with a radioactive molecule that binds tightly to a membrane receptor. The screening system then consists of the measurement of the inhibition of the radioactive ligand binding or the displacement of the bound radioactive ligand from the receptor site by the drug candidate.

Cell culture screening systems have become commonplace over the past few years. Single mammalian cells growing in culture medium under controlled conditions are maintained in vitro. Most recently, cell lines that have incorporated the gene sequence (human genome) of the receptor and express the human form of the receptor have been incorporated into primary in vitro screening strategies. This strategy and technology eliminate the uncertainty of the animal receptor mimicking the human receptor form. In addition, it allows for highly improved specificity of the drug candidate's binding capabilities to the targeted human receptor and reduced binding to receptors in other parts of the body, thus potentially leading to improved efficacy and reduced side effects.

Beyond the cell stage of primary screening, isolated tissue strips of blood vessels, skeletal muscle, or heart muscle can be prepared under controlled conditions. While the tissue is suspended in an appropriate medium to ensure its survival, actual contraction or relaxation of the tissue can be measured mechanically. Information obtained from this in vitro, isolated tissue preparation can be valuable in determining a drug candidate's potency in eliciting an actual functional response secondary to receptor activation or inhibition.

High-volume screening is conducted using another approach to in vitro testing, that is, enzyme inhibition. The techniques and objectives are similar to those described for plasma membrane-bound receptors. However, an enzyme exerts its effect on a molecule to convert it to a different substance, without altering or destroying the enzyme in the process. The converted substance then has an effect on the biological system. A classic example of this approach is the identification of angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertension. The ACE inhibitor blocks the enzyme's ability to convert angiotensin I to the active form angiotenin II. The vasoconstrictor effects of high levels of the angiotensin II and its ability to raise blood pressure are reduced. Most recently, compounds are being tested in in vitro screening systems by many pharmaceutical companies that would prevent the enzyme that converts acetylcholine in the brain to inactive metabolites. By doing so, it is hypothesized that the brain tissue levels of acetylcholine of Alzheimer's disease patients would be elevated and, thus, improve the cognitive function and quality of life of these patients.

Only a few of the many test systems that can be used in vitro have been described. The strategy is to develop a "high-volume" screening assay capable

of screening large numbers but small quantities of compounds in the most time and cost-efficient manner possible. The primary screen should be carried out in one or two selected doses initially, usually performed in triplicate tubes or plates per dose to reduce variability. If activity is found, it is confirmed using a large number of doses and more replicates per dose to establish a dose-response curve. Potency is established comparing a standard that is *known* to possess the activity in the specific test system.

Once pharmacological activity has been identified and confirmed in vitro, the drug candidate is next evaluated in a whole animal screening system. The initial in vivo testing is performed in small animals, usually rodents, for several reasons. There is an abundance of historical information on rodent in vivo testing systems, and they can be performed at low cost. In addition, tests performed in rodents can be analyzed with small amounts of compound. Initially, the pharmacologist may choose to perform the in vivo test by intraperitoneal injection to ensure that the compound is delivered to the body. This cannot always be assumed following oral administration based on the lack of information on the compound's intestinal absorption or the effect of the liver on metabolism of the drug as it is first transported by the hepatic circulation (first pass effect) at this early stage of drug screening. Any biological activity observed with intraperitoneal administration will be followed by oral administration if it is the preferred route of administration in humans.

The overall objective of all whole animal studies is to develop a model that most closely mimics the human disease state. Fundamental biological differences among animal species; a lack of understanding of the human disease state on the part of the scientist; and differences in absorption, metabolism, and excretion of drug molecules make this objective difficult to achieve. In the field of type I diabetes, two animal models have been developed: (a) a diabetes-like disease model produced by destroying the pancreatic cells that produce insulin by injections of the chemicals alloxan or streptozotocin and (b) diabetic animals with genetic deficiencies in insulin production and secretion. Much work has been done in animal models of hypertension such as genetically hypertensive rats and dogs, hypertension produced by wrapping the kidneys or clipping a renal artery, or hypertension induced by excessive salt intake. Great efforts are underway to develop transgenic animal models of human disease states. The technique involves identifying and isolating the gene sequence that may be responsible for producing the human disease state and injecting this gene sequence in animals to either knock-out a target site or cause an overexpression of a protein that may cause the underlying disease state. Most recently, a model of cystic fibrosis in mice has been the only successful model to be produced and utilized in drug discovery.

Pharmacologists have invested a great deal of effort to develop animal models of human central nervous system (CNS) disorders. This area of drug

discovery is of particular difficulty based on the overall complexity of the brain itself and the overall lack of knowledge of the human disease state. A variety of tests have been developed through the years that measure the effect of drugs on a particular subset of animal behavior such as the ability to learn a task by spatial, visual, or auditory stimuli; the ability to avoid electric shock; or the ability to gain a reward by learning a task. Such tests have been developed across a wide range of animal species including rats and nonhuman primates. Behavioral pharmacologists attempt to evaluate compounds in whole animal behavioral tests and, based on their biological profiles, make judgments as to whether they can be expected to act as antipsychotics, anxiolytics, antidepressants, hypnotics, or cognitive enhancers in human disease. Drug discovery in Alzheimer's disease, for example, has been slow since the underlying cause of the disease in humans is still unknown and, therefore, attempts to mimic an unknown pathophysiological state have proven challenging and frustrating. Data from postmortem examinations of Alzheimer's disease patients have shown a reduced level of the neurotransmitter acetylcholine in the frontal cortex and an excessive amount of plaque deposits compared to normal, age-matched patients. Therefore, attempts are underway to develop animal models showing these same abnormalities and to identify compounds that can treat the symptoms of the disease state (memory, quality of life, etc). We will be well into the next decade before compounds are tested in humans that can either slow or reverse the progression of Alzheimer's disease due to the limitations in valid animal models.

Once in vivo biological activity has been established, the drug candidate undergoes secondary biological screening. It is compared to known standards that are available and have proven to be effective in the treatment of human disease. Potency of new compounds is assessed relative to the known standard along with the degree and duration of the activity. The objectives of the standard comparison animal studies may vary depending on the clinical need or marketing profile desired. These objectives may include enhanced potency, a longer acting compound than those currently on the market, a compound showing a reduced side effect profile, a compound that may treat a population of patients resistant to existing therapies, and/or a compound that may have comparable activity to the marketed standard but can be produced and sold at a reduced price to managed care providers.

The overall objective of the pharmacologist is to determine the biological profile of a compound in in vitro and in vivo systems that may be predictive of pharmacological activity in humans. This has proven to be a major challenge in the pharmaceutical industry in attempting to ensure safe but effective drug treatment driven by preclinical drug discovery programs based on cellular and animal models mimicking the human disease state.

V. TOXICOLOGY AND BIOANALYTICAL CHEMISTRY

It may be considered appropriate to group preclinical toxicology and bioanalytical studies together since (a) many regulatory agencies, including the FDA, have indicated that the toxic effects and pharmacokinetic profile may be the most important information on a drug candidate; (b) unlike preclinical chemical synthesis, biochemistry, and pharmacology, both toxicology and bioanalytical studies are conducted under strict regulatory guidelines (Good Laboratory Practice); and (c) toxicological and bioanalytical studies are often conducted concurrently.

By definition, the purpose of toxicology studies is to administer high doses of the test compound, which will induce toxic effects to the animal model, identify the most sensitive organ of the body, and to predict the maximum dose that does not produce toxicological effects. Again, initial studies are performed in rodents because of the lower cost of the animals, care and housing, and the amount of compound required. Toxicological studies must be of a certain duration to expose humans to the compound. Standard FDA guidelines state that in order to administer one to three doses of a new substance to humans, a minimum of 2 weeks of administration of the substance to two animal species is required. If the drug is to be given to humans for 1 week but less than 3 months, the compound must be given by the ultimate route of administration for 3 to 6 months. For new investigational drugs to be used on a chronic basis in humans, 1- to 2-year toxicity studies are performed correlated with plasma concentrations of drug in two species (usually rat and dog). Carcinogenicity studies may also be required involving lifetime administration to two species if the drug is anticipated to be administered chronically in humans.

The toxicological profile also include mutagenicity studies in vitro in a variety of systems and, possibly, studies addressing the intended use of the drug in humans (pediatric or neonatal, administration in pregnant women or nursing mothers). Mutagenicity studies assess the potential for the drug candidate to alter the genetic material of microbial or mammalian cell cultures. This may be measured by the ability of the microbial system to grow in a particular medium or the ability of mammalian tissue to repair any damage to its genetic material. If any evidence of these measurements are observed, the drug may be classified as mutagenic. Although in vitro systems are limited in their ability to correlate undesirable genetic effects in the test tube to the probability of being mutagenic or causing cancer in the intact animal, suspicion is automatically focused on the drug candidate. Most pharmaceutical corporations would not pursue a drug candidate demonstrating mutagenicity, and such results are considered high hurdles to overcome with regard to regulatory approval.

Toxicological studies follow strict protocols based on Good Laboratory Practices (GLP) and are carried out in two basic phases. The in-life phase in-

volves the administration of the compound by the route the drug would be ultimately administered in patients. At least three doses are administered, one dose that is clearly toxic to the animal (loss of weight, reduced food intake, overt signs), one dose that elicits no toxicity (no-effect dose), and one dose that is between the toxic and no-effect dose. Input into the protocol design and review by the pharmaceutical development scientist is critical. The use of a toxicological dose form, usually a solution or suspension, must be designed according to the knowledge generated in the preformulation laboratory. A uniform suspension or solution of the test compound that is physically and chemically stable over the entire toxicological testing period must be assured. The animals are observed and weighed, and blood and urine (bioanalytical) studies are performed at appropriate intervals designated by the protocol. Behavioral changes and overt signs of toxicity are noted (excessive salivation, vomiting, diarrhea, piloerection). If any animal dies during the study, the time and circumstances are recorded.

The animals are sacrificed in a humane manner at the end of the in-life phase of the toxicity studies for pathology evaluation. A complete necropsy is performed by a toxicologist and/or pathologist with the internal organs examined by gross examination to correlate with tissue dose with potentially toxic effect in various tissues. Any evidence of deviation from normal is noted, each organ is weighed and samples are taken from various sites from each organ for histopathological preparation and examination. The toxicology and histopathology reports are compiled and submitted to the regulatory agency. If dramatic differences in the toxicity profile of the two species are evident, a toxicity study on a third species (usually monkey) is required before the compound is allowed to be administered in humans.

Toxicology and pathology studies are both expensive and time consuming. A cost of 1 to 2 million dollars is not unusual for 1-year toxicology studies in rats and dogs, with up to 3 years elapsing before the final report is submitted. The cost also includes the quantity of bulk compound used for the toxicity studies, which could exceed 50 to 70 kg. Once the toxicity study is completed, the toxicologists, pharmacologists, pharmacists, and clinical investigators meet to determine the first dose to be administered to humans, dosing rate, route, frequency of dosing, etc. This projection may vary among companies, but it is not unusual for the first human dose to be a small fraction of the no-effect dose of the most sensitive species (approximately 10%). In addition, it is not uncommon for companies such as Merck and Co. to take three to four of the same therapeutic series to phase I clinical trials and choose the best drug candidate for more advanced and expensive clinical development. One cannot be certain which species will be the best predictor of humans.

Investigations on the absorption, distribution, metabolism, and excretion of the compound are commonly performed in rats and dogs, the same species in

which pharmacological and toxicity studies were performed. In the bioanalytical study program, the compound is administered by the ultimate route of administration (intravenously or orally); and samples of blood, urine, and feces are collected to determine the amount of drug absorbed into the animal, the amount excreted and the rate and route of excretion, and the extent of hepatic first-pass metabolism. Measurements are made by sensitive assays capable of measuring small amounts of substance in blood serum or urine. Many groups prefer to use a radioactively labeled compound for the metabolism work since it cannot only measure the pharmacokinetic profile of the parent compound, but can also detect any metabolites produced by the different species. However, other sophisticated techniques such as solid-state nuclear magnetic resonance, liquid chromatography, and mass spectrometry are being utilized to determine potential metabolites of the parent compound. The bioanalytical scientists are interested in determining (a) the peak levels of the drug at various doses and the time it takes for the drug to reach peak levels; (b) how rapidly the drug is eliminated by the body as measured by the plasma half-life; (c) the total amount of material in the blood (area under the elimination curve); (d) the identity of any metabolites, substances resulting from the conversion of the parent compound into a biologically active compound by metabolic processes of the body; and (e) comparisons of the pharmacokinetic profile of the compound in the different species (including rate of elimination, biliary cycling, and fat deposition). In addition to the parent compound, any metabolites identified must be characterized as to their potential pharmacological or toxicological effects. The metabolites are often patented along with the parent compound in the event that the metabolite turns out to be the active form. Most important is the significant validity of the toxicology studies if it is determined that humans produce the same metabolites as the animal species.

VI. PRECLINICAL PHARMACEUTICS

The field of pharmaceutics has grown immensely in the last 20 years and is now recognized as a major contributor to drug research and development programs in both academic and industrial settings. Although a relatively new discipline when compared to others such as chemistry, biology, and pharmacology, pharmaceutics has become well established within the scientific community. Pharmaceutic activities encompass the entire range of drug development from discovery through the design of final marketed dosage form. The pharmaceutics scientists are formally trained in both the basic sciences such as pharmacology, medicinal and physical chemistry, biochemistry, and physiology and applied sciences including pharmacokinetics, pharmacodynamics, and chemical engineering principles applied to drug transport. Specifically, pharmaceutics scientists are trained to understand and investigate factors affecting the absorption,

distribution, metabolism, and excretion of pharmacologically active agents. Preclinical pharmaceutics is defined here as a discipline of two interrelated functions: traditional preformulation/physical pharmacy and biopharmaceutics/pharmacokinetics. The marriage of these disciplines gives preclinical pharmaceutics a unique perspective on the drug development process. The first branch, preformulation/physical pharmacy, determines the physical and chemical properties of neat drug substance including solubility, stability pKa, and lipophilicity. The second branch makes use of this information to study the relationship of the physicochemical characteristics with in vitro drug behavior in delivery of drugs to the body. The output from this function is a summation of all preclinical conclusions and serving as the basis for design issues of first-time-in-humans studies.

Preclinical pharmaceutics serves a dual role within the preclinical drug development process. First, by working closely with research and discovery colleagues, information is provided that serves as an integral part of the decision-making process facilitating and expediting the selection of optimal compounds at an early development stage. Second, by using the information gained from previously mentioned experimental approaches, dosing strategies are recommended, which aid formulation scientists in developing the clinical and commercial drug delivery system, maximizing bioavailability and therapeutic performance of the chosen drug candidate.

The traditional preformulation/physical pharmacy experiments are well known and have been outlined previously in numerous texts. More recently, animal and cell culture biopharmaceutic experiments with pharmacokinetic analysis of the data have emerged as a competency within the field of pharmaceutics.

Pharmaceutic experimental research involves using in vitro and in situ models, descriptive of drug absorption in vivo, as tools aiding in the discovery of new chemical entities suitably bioavailable after oral administration. Models include in situ single-pass intestinal perfusion, chronic fistulated intestinal loop systems, and in vivo rat everted intestinal ring or monolayers of human colon adenocarcinoma cell line (CACO-2). The rat in situ single-pass intestinal perfusion and chronic fistulated loop systems base permeability calculations on steady-state disappearance of compound from the intestinal lumen. The rat everted intestinal ring method uses accumulation of the compound in vitro to determine drug uptake rate. The CACO-2 cells are grown on membrane filters and mounted in diffusion chambers. The rate of compound appearing in the receiver compartment is the basis of the permeability measurement. Each of these models has been shown to produce relatively reliable determinations of intestinal permeability and potential limitations to absorption.

When these results are integrated with the extensive in vivo data generated by both bioanalytical and drug safety/toxicology groups, the results provide a

wealth of information for potential Investigational New Drug (IND) candidates and meaningful feedback to the drug discovery groups. In addition, a thorough knowledge of both the potential site(s) and extent of absorption and any limitations due to the physicochemical properties of the drug candidate enable the formulation scientist to develop rationally and more quickly an optimized dosage form.

Beyond the pure basic pharmaceutics role, the pharmaceutical development scientist must recognize and initiate activities in related development functions as the research compound moves toward IND submission. Once again, the pharmaceutical development scientist is nicely positioned to facilitate initiation of activity on formal stability protocol development and conditions, adequate bulk active ingredient supply for clinical studies, and necessary noncommercial dosage form development required for clinical pharmacology studies, such as absolute bioavailability determination, or other studies to establish the complete pharmacokinetic profile.

VII. SUMMARY

This chapter provided individuals who have expertise in pharmaceutical development and formulation a general overview of the interactions and integrative processes between the various preclinical functional groups and disciplines, the strategic approaches and challenges encountered in the preclinical drug discovery process, and the role of the preclinical drug discovery program in identifying drug candidates for the therapeutic treatment of human disease. It is imperative that drug discovery also be tightly integrated with the next steps in the pharmaceutical development process: (a) providing clinical investigators with a drug candidate that addresses a clear clinical need and (b) providing the product managers with a drug that is truly differentiable from the existing marketed products (unique mechanism of action, ease of administration, competitive product pricing, etc). The drug discovery process should be viewed as providing the innovation to address clinical needs for treating debilitating diseases and products that can eventually have an impact on company revenues and profits in a positive and significant manner. The key responsibility of the preclinical development expert toward internal customers is the necessity for the smooth transition in clinical and product development. However, as scientists and management involved in the drug research and discovery processes strive to produce innovative therapeutic approaches, they should not lose sight of the ultimate goal, treatment of disease, and the ultimate customer, the patient.

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3

Clinical Development of a New Chemical Entity

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I. INTRODUCTION

Hospital pharmacies are often involved in the support of clinical research programs initiated by academic physicians in their hospitals which may be sponsored by departmental research funds or the National Institutes of Health. The study of new chemical entities, however, is normally under the direction and control of one of the major pharmaceutical companies. The clinical development plans from such companies are designed to elucidate the maximum tolerated dose of a compound in humans, determine the effective dose range based on a balance of efficacy and safety, define its comparative efficacy against other compounds available for the same indication, and fully investigate the mechanism of action, pharmacodynamics, and pharmacokinetics of the compound. In addition, studies in special populations (e.g., patients with hepatic or renal impairment) will often have to be performed, drug interaction studies will be required for expected concomitant therapies, and, with the recent focus on the cost of health care, pharmacoeconomic studies will play an important role in securing the access of a new drug onto a hospital formulary.

Clinical plans are generally divided into four major phases called phase I, II, III, and IV. During the whole program, appropriate special studies will be conducted depending on the available safety information to justify studies in patients with particular organ impairment. Clinical trial designs are most commonly of a parallel group design, but may utilize crossover and Latin square designs. Proof of efficacy normally requires a placebo control unless ethical considerations prevent its use (e.g., antiinfective studies). In some countries, and certainly to support pricing, active control studies are also conducted in the later stages of the clinical development program. Because of the vagaries of treating individual patients, as against, for example, treating rats in preclinical studies, the protocols that are designed need to cover most of the expected events in clinical medicine that can occur with the patients, disease, and the study. The protocol designs, therefore, often have lengthy inclusion and exclusion criteria, precise details of permissible concomitant medications, with extreme detail on the methodology of how the is study to be conducted. These protocols are often voluminous and daunting, but it is only by thoroughly thinking through the potential problems in advance, and deciding which exceptions can be allowed and when deviations could seriously confound the study and weaken the analysis, that ensures the study will satisfactorily answer the scientific question. Some of these issues, therefore, will be briefly addressed in the rest of this chapter.

II. THE DIFFERENT PHASES OF CLINICAL DEVELOPMENT

A. Phase I

The phase I program includes the first studies of a new drug to humans, which can only be performed after a minimum level of toxicology, toxicokinetics in

animals, pharmacology, mutagenesis and other preclinical studies have been performed. In the United States, such data are submitted to the Food and Drug Administration (FDA) in a document termed the Investigational New Drug (IND). This submission also contains details of the initial proposed protocols. Based on pharmacokinetics and pharmacodynamic considerations in a number of different species of animals, the initial study is normally a single dose, rising dose study whereby volunteers (patients often have to be used for some products, e.g., cytotoxic agents) receive single doses of the new chemical entity. The starting dose will be a large factor below any expected efficacy (e.g., 1% of the expected therapeutic dose) so that any unexpected adverse events will be observed at the lowest possible dose. Each volunteer will receive only one dose, and the study will normally be placebo controlled at each dose level. Only after each dose level is successfully completed, with no serious adverse effects, will the dose be escalated to the next level, and normally no volunteer can receive more than one dose. As a protocol proceeds, new volunteers gradually receive increasing doses until the necessary efficacy is observed and/or safety becomes an issue. During these studies, plasma samples are normally collected to determine the initial pharmacokinetics in humans to get some indication of the distribution, metabolism, and elimination of the compound.

The next stage is the initiation of multiple dose tolerance (MDT) studies in which volunteers receive the compound for 7 to 14 days, again using a range of doses. It is hoped that these studies will show that the drug does not accumulate with multiple doses, and that pharmacokinetic analysis of the metabolites will not show any saturation of metabolism. As with the single dose study, the MDT study should be placebo controlled to interpret any pharmacodynamic effects, and to put the reporting of adverse events into perspective.

B. Phase II

Once a safe dose range for the compound has been determined, the drug will be tested next in patients with the intent of determining the effective dose range. Often, initial pilot dose-ranging studies are conducted in a small patient population to determine the initial dose range. Once this potential range is determined, much larger dose-response studies are conducted during the phase II program. Such studies should have a fairly wide dose range (e.g., 10 mg, 100 mg, 500 mg as against 100 mg, 200 mg, 300 mg) because it is possible to interpolate responses between doses but not extrapolate outside the doses studied. Dose-response studies may produce confounding results if the doses selected are too close together, and the appropriate multiple between the selected doses can be estimated based on the interpatient pharmacokinetic variability observed in previous studies. Dose-response studies are normally placebo controlled and of parallel group design (see later). The inclusion and exclusion criteria will often be very restrictive so as to reduce the variability of extraneous factors, which could cause a problem with interpreting the final results of

the study. It is not uncommon for such studies to have 100 to 150 patients in each treatment arm and, when studying three different doses and a placebo arm, there may be a requirement for up to 600 evaluable patients. As these are the initial studies in patients, a large amount of laboratory testing and safety evaluation will have to be made in addition to the efficacy measures; hence, even these early studies are an expensive and risky undertaking. Most studies have used the traditional randomized dose controlled design, but randomized concentration-controlled studies are increasingly being considered. Such studies have logical problems, requiring systems for rapid pharmacokinetics analyses of samples, but usually require a smaller number of patients, and may be very useful in those diseases that have limited numbers of patients to study.

The phase II program will not only study the dose-response characteristics of the drug, but also should address the dose regimen (e.g., determine whether the drug should be given once, twice or three times a day, or whether the drug can be given as nighttime dosing vs morning dosing). If the phase II protocols are adequately designed and of sufficient power, then regulatory agencies will increasingly allow such studies to be regarded as a pivotal study for proof of efficacy, assuming, of course, that the results are positive.

C. Phase III

Before commencing phase III, the results of phase II should have identified the proposed dose regimen, dose range, time and onset of action, etc.

The phase III program is essentially the confirmation of efficacy in much larger patient populations and the determination of a fuller understanding of the safety profile of the compound. Long-term safety studies will be initiated during this phase, and during what is often termed phase III, additional studies will be initiated to help support the marketing and pricing of the compound. Because phase III, therefore, requires long-term studies in large numbers of patients, it is essential that the pharmaceutical company has an accurate definition of the dose and regimen to be studied. Much time and money are wasted by companies commencing phase III before completion of the analysis of the phase II program. Generally, the efficacy studies that are required for regulatory approval of a compound need to be placebo controlled (exceptions include antibiotic studies during which another approved antibiotic will be the control) and may utilize one or two doses of the compound at the expected doses to be used in the labeling. The duration of the studies will depend on the disease and the study and will range from 10- or 14-day studies of an antibiotic (with longer follow-up) to 2 years for studies of lipid-lowering agents, which will eventually be approved for long-term therapy. The exclusion criteria of the protocols should be more relaxed to include a study population that is closer to that which will eventually be the prescribed compound. This will also enable more elderly patients to be entered so that the efficacy and safety in this increasingly impor-

tant population are adequately studied. The program should also ensure that different ethnic races are included in the study, which can be especially important, for example, for the study of antihypertensive agents. There are now FDA regulatory requirements to ensure that an adequate number of female patients are studied during the clinical programs. Management of these studies requires not only checking that inclusion and exclusion criteria are being followed, but that the necessary patient population profile is being screened and entered.

Once the placebo-controlled study program is under way, then open-label, long-term safety studies will usually be initiated, (often to continue therapy in patients as they successfully complete the pivotal phase), so that patients may continue therapy indefinitely or for a further 1, 2, or 3 years. Although efficacy data may be collected, the primary aim of such long-term studies is to determine the long-term safety of the compound and especially to elucidate any unexpected side effects that occur after a long period of therapy. Depending on the compound and the study, therefore, extensive radiographic, electrocardiogram (ECG), electroencephalogram (EEG), and laboratory tests may be conducted at 3- or 6-month intervals. Generally, having established a program that will obtain regulatory approval, clinical plans will also initiate those studies that will assist marketing and demonstrate benefits so that the new drug is accepted by hospital formularies. Such studies may target health economics or fundamental new research areas and will often be controlled against one of the major competitors in the market place. As it is always more difficult to demonstrate a significant difference versus an active compound than to a placebo, these studies are often very large, running into the thousands of patients, but will often have an important scientific question to answer if the results are intended to be used in promotional campaigns.

D. Special Studies

After completion of the multiple-dose tolerance studies during phase 1, and before completion of phase III and submission of a New Drug Application (NDA) to the FDA regulatory authority, other important studies must be conducted in parallel to the large dose-response and proof-of-efficacy programs. Such studies will evaluate possible drug interactions with the most frequently expected concomitant medications; will further address the pharmacokinetic profile of the absorption, distribution, metabolism, and excretion of the compound; and may often determine tissue levels (e.g., antibiotics). Other studies may examine the pharmacodynamics and elucidate the mechanism of action, and, assuming that the compound is an oral formulation, mass balance will be conducted using a parenteral formulation to elucidate the bioavailability of the oral compound. As much of the phase II and phase III program may be conducted with an oral formulation specifically designed to make trial supply blinding easy, bioequivalence studies will have to be conducted against the intended

final market formulation. Additional studies will also be required to determine the pharmacokinetics and pharmacodynamics in the elderly or pediatric populations, and depending on metabolism, excretion, and toxicology profile of the compound, special studies will often be required in patients with renal or hepatic impairment. The successful completion of these special studies in the humans contributes to a clear understanding of the pharmacokinetics, pharmacodynamics, and other properties of the compound and is important to the labeling that it is ultimately approved.

Once all these studies have been completed, the company must not only report each study individually, but also compile integrated summaries of the efficacy and safety of the compound, which requires complex analysis of very large databases. The submission is termed a New Drug Application in the United States and a Marketing Authorization Applications (MAA) in Europe.

E. Phase IV

The compound enters phase IV clinical development once it has been approved. Generally, such studies are conducted to provide market support and may have to be initiated rapidly if a competitor comes out with a new claim or indication. Some phase IV studies may be required only for publication purposes and are usually conducted for the approved indication, or may be exploratory studies for potential new indications.

F. Phase V

Phase V has different interpretations in different companies, but I use it to define additional studies that will ultimately be submitted to regulatory authorities for approval of new indications, formulations, etc. Such study protocols may, therefore, have all the complexity of Phase II and III protocols.

III. CLINICAL TRIAL DESIGNS

As previously mentioned, clinical trials may be designed to answer many issues of safety and efficacy; the objective may be to determine the compliance, effective dose range, duration of action, health economic issues, or quality of life. Different trial designs are required to answer different objectives, and it is important that any one study does not try to answer too many questions; otherwise, the necessary compromises that have to be made will interfere with the different assessments. The study protocol must determine the primary and secondary efficacy criteria, establish an adequate baseline and allow necessary washout of any preceding medications, and ensure that assessments are performed at appropriate intervals. For some compounds and some indications, it may also be necessary to study the efficacy just before dosing (trough) and at

the expected maximum concentration (peak). Determination of the intrapatient variability between the peak and trough efficacy can help elucidate the appropriate dosing interval.

Apart from the long-term safety studies, which by necessity are usually of open design, most of the preceding studies will utilize a double-blind controlled design. To compare the various regimens, it is possible to use a parallel group design, crossover, or Latin-square design. Assignment to dose may be fixed, by forced titration, or by optional titration, depending on response.

A. Randomized Parallel Group Fixed Dose

After the necessary baseline period, this design will immediately start patients on a randomized fixed dose of one of the regimens to be studied (Fig. 1a). This assigned dose will continue throughout the entire duration of the study, and no alteration in the dose regimen will be allowed.

B. Randomized Parallel Group Forced Titration

This design (Fig. 1b) uses a similar process to the fixed dose design, but it is used when it may not be safe to start patients on a high dose of the compound, and patients need to be titrated from a lower starting dose (e.g., studies of compounds for the treatment of epilepsy). Designs are intended to ultimately have patients randomized to receive different doses of the compound, but every patient initially starts therapy with a low dose as shown in Fig. 1b. The titration steps up to the higher doses should occur at fixed time points, and the provision of clinical trial materials must ensure that patients and investigators are blinded as to who is titrated to an increase in dose.

C. Randomized Parallel Group Optional Titration

The optional titration design (Fig. 1c, will ensure that all patients initially start on the low dose of the compound, but, compared to the previous design, patients titrate to higher doses depending on the response and safety assessment at the low dose(s). Some designs may allow all patients to be titrated to the top dose unless safety issues prevent an increase of the dose, and other designs may require patients to be titrated only if a defined efficacy response is not met at the end of each treatment period. Generally, such designs only allow the optional dose escalation to occur at specific time points, which not only helps control the variation that can occur during the study, but also facilitates the packing of clinical trials materials. Such designs are useful because they more truly mimic the eventual clinical situation whereby patients are titrated to maximum effect. Such data can supplement the fixed-dose parallel group dose-response study in determining the proportion of patients that require the differ-

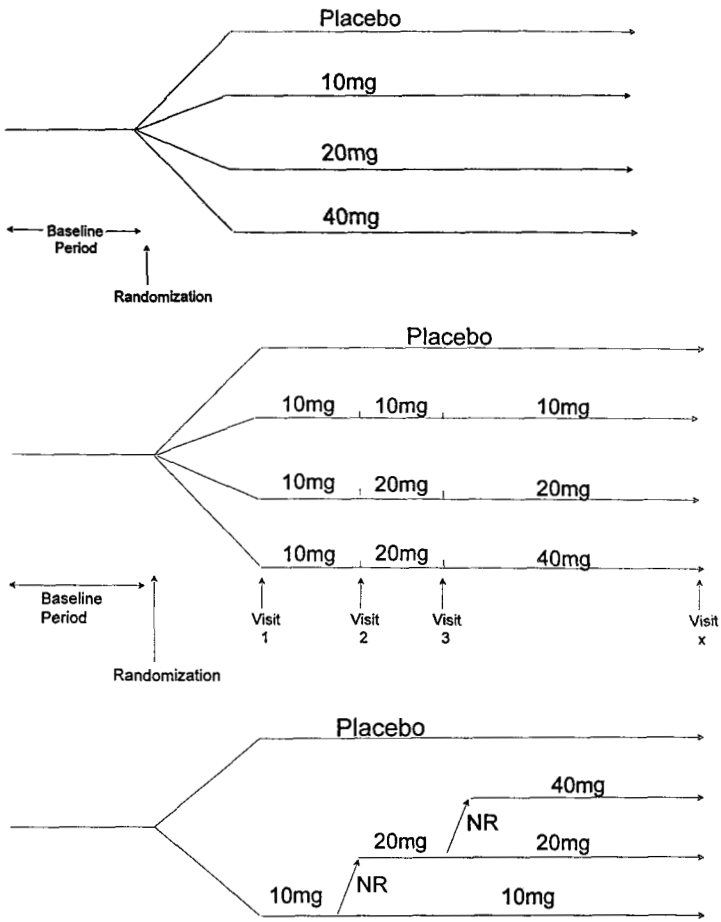

FIG. 1 Examples of randomized parallel group design. (a) Classic parallel group, fixed dose design. (b) Parallel group, forced titration, where all patients start on a low initial dose and have mandatory titration to randomized dose. (c) Parallel group, optional titration, where all patients start on a low initial dose, and nonresponders (NR) have their dose increased. Responders continue on the lowest efficacious dose.

ent doses of the compound to achieve a similar response, and are only utilized when two active compounds are being compared.

D. Randomized Crossover Design

The crossover design (Fig. 2) enable intrapatient assessments to be made, but it is confounded by possible carryover effect of the first phase into the second

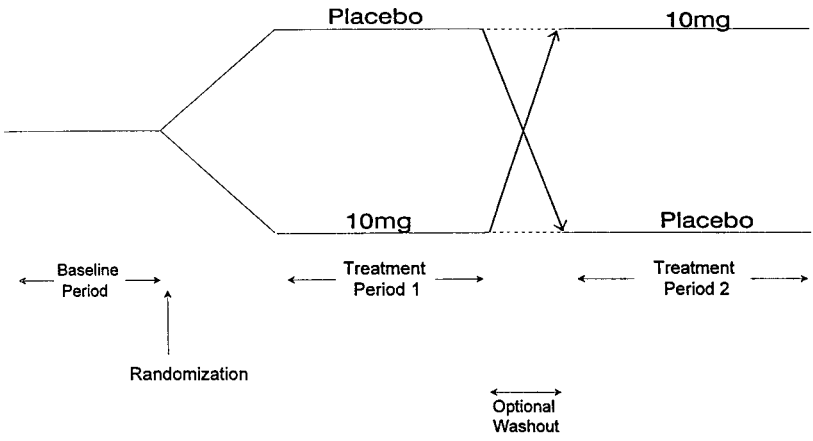

FIG. 2 Crossover design. Patients are crossed to the alternative therapy and treated for the same duration of time. There may or may not be another washout period at the time of crossover.

phase, and by a time effect (e.g., if the disease spontaneously improves, or is getting progressively worse). For these reasons, such designs are less popular now but have the advantage of requiring a lower number of patients and are useful in rare or more stable illnesses. Decisions need to be made as to whether a second washout period is used between the two treatments, and if so, what will then be used as a baseline for each treatment period. Alternatively, each of the treatment arms can be of sufficient duration that by the end of the second phase, any carryover effect from the first phase should have been eliminated and a second washout phase is not required. Although crossover studies require fewer patients, patients must be able to tolerate the study for at least twice as long as a normal parallel group design, and this may result in a greater number of dropouts during the study.

E. Randomized Latin Square Design

Fig. 3 shows an example comparison of three treatments whereby six differing ordered dosing regimens utilizing a crossover design ensure an equal balance of each possible dose order. Such a design is more able to eliminate the effects of a previous treatment period, or of a time effect. When properly conducted, with adequate duration of therapy during each phase, such designs are extremely powerful and require a greatly reduced patient population; furthermore, they have been accepted by or known to be acceptable to some divisions of the FDA as pivotal proof of efficacy studies.

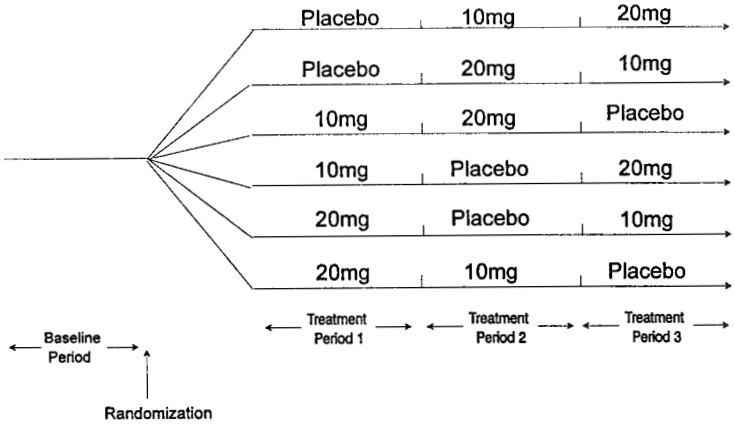

FIG. 3 Latin square design. Ensure an equal balance of each possible dose order.

IV. CONTROL AGENTS

In addition to the common placebo comparator, active control agents are often used during the clinical research program. To secure a supply of active compound, it is usually necessary to obtain the support of a competitor company to provide the agent and matching placebos; alternatively, the pharmaceutical company will have to manufacture its own supply and conduct dissolution and possibly bioequivalency studies against the competitor product that is approved and marketed. If it is possible to manufacture the active control, then it is often possible to have tablets or capsules of similar appearance to the new drug in the study but, if the active compound requires tablets or capsules of different color, size, or marking, a "double-dummy" technique has to be utilized. Fig. 4 shows an example of a double-dummy technique whereby each

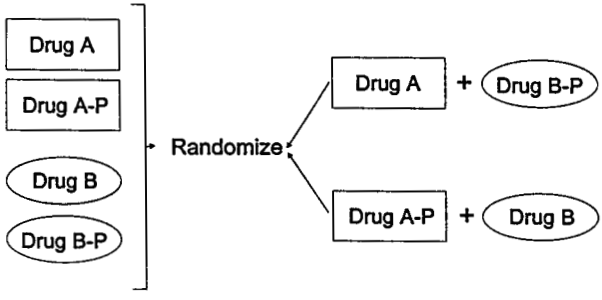

FIG. 4 Example of dispensing with a double dummy design. Drug A-P is a placebo, identical to drug A. Drug B-P is a placebo, identical to drug B.

patient receives one tablet and one capsule, but only one of the two administered formulations contains an active preparation. Such design obviously requires patients to take a greater number of tablets or capsules, which increases the complexity of the study design and clinical trial packaging , and can lead to reduced patient compliance. It is important to consider the source of the active control medication if multinational studies are being considered, as it is usually necessary to obtain government approval for the active control formulation, as well as the experimental drug. It is not unknown for the supposedly similar marketed product to have different excipients or coloring agents, for example, in different countries; this may prevent the use of an active controlled purchased from one country being utilized in other countries. To overcome such difficulties, detailed preplanning is required to order and obtain the necessary supplies and regulatory documentation from the pharmaceutical company that is manufacturing those supplies.

V. MULTINATIONAL STUDIES

Because of the cost of conducting clinical research, companies are not repeating clinical studies in individual countries, but are sharing the centers used in multicenter studies across countries so that multinational studies are common. Generally, studies are conducted in the United States are only shared with Canadian sites, but within Europe, a study may be conducted within a large number of countries.

The problems relating to use of active control medications in different countries have already been discussed. In addition, all clinical trial supplies need to be packaged with the labeling translated for the country of use. There are restrictions on the rules of importation and the necessary date or repeat testing required. In addition, different custom importation requirements and problems related to international shipments mean that the managers of such studies need to provide much longer lead times. From the investigator or pharmacist perspective, it is necessary to provide more advanced warning of potential additional resupply requirements than when conducting the study in the same country from which supplies are originally supplied.

VI. PATIENT COMPLIANCE WITH MEDICATION

The accuracy of the results of the clinical trials depend on whether the patient takes the study medication. This can be more onerous, for example, in studies utilizing a double-dummy technique, in which patients may have to take twice the number of tablets/capsules that they would usually take to maintain the blind of the study. In studies in which the patient cannot daily perceive an

advantage, (e.g., lowering lipids, long-term prevention studies), the patient can honestly forget to take the medication. One advantage of a placebo baseline phase is that it provides an opportunity to screen patients for compliance, and hence not randomize the poor compliers to the study. It is important that investigators assess compliance during the baseline phase and agree in the protocol as to what is an acceptable compliance factor for randomization.

VII. EMERGENCY CODE BREAKS

It is necessary to provide a means of breaking the code in double-blind studies in emergency situations. In some countries (e.g., the United Kingdom), it is also necessary to break the code for all serious adverse events rather than reporting them to the regulatory agency in a blinded manner. The FDA does not currently require codes to be broken, but proposed new regulations will probably require this. Generally, code breaks for the regulatory reporting of serious adverse events should be conducted by the clinical safety department within a company, and the study monitor should ideally remain blind to the code break. If there is an undue increased and unexpected incidence of an adverse event, then the clinical safety department will have internal procedures for informing the company clinical staff.

Returning to the emergency code break for the investigator, the supplier of the medication should provide sealed lists to the investigator and the pharmacist. The procedure must allow the code to be broken for one patient, without seeing the results for other patients. Some trials use envelopes, but most automated systems now use preprinted cards that allow the patient number to be "popped" (as in a Christmas Advent Calendar). Whenever an emergency code break is performed, the reason and date must be recorded. In addition, all such code break materials need to be collected and reviewed at the end of the study to ensure that the study blind was maintained.

VIII. REQUIREMENTS FOR DRUG STORAGE

The investigator needs to work closely with their pharmacist for arranging appropriate storage and dispensing of the study medication. The physical volume of such medication can be large.

If a study is not being conducted at a hospital, and the physician is dispensing the supplies directly, the supplier must check and ensure that there are appropriate storage conditions with secure limited access, and that the drugs are stored according to the controlled environment on the label. It may be necessary for the investigator to have a lockable refrigerator in order to adequately store certain products, for example. It is important that such a refrigerator is not also used to store lunch as well!

IX. CONDUCT OF A CLINICAL STUDY

The process of planning, managing, implementing, monitoring and reporting a study may be summarized as follows:

a. Clinical Plan	- Identify the studies required for •Registration •Marketing - Identify the comparative agents (active/placebo) to be used - Identify and define the dose regimen and dose range
b. Individual Study Design	- Agree on scientific questions and objective to be answered - Write protocol with involvement of principal investigator, biometrics, clinical pharmacy (and often many other departments)
c. Identify Study Sites	- Usually based on the experience of the investigator, ability to conduct studies to Good Clinical Practice (GCP), etc. Strategic issues as to which countries are to be used are also considered.
d. Obtain Investigational Review Board (IRB) Approval	- Ethical committee approval obtained in Europe.
e. Investigator Meeting	- A meeting conducted at the start of the study at which the protocol, case report forms (CRFs), drug supply details, and other procedures are explained to all the investigators. After this meeting, drug supplies are supplied to the sites.
f. Monitoring of the Study	- The company will utilize contract research associates (CRAs) to regularly monitor the investigator site, review the (CRFs), check the data against original source documents for accuracy, identify and resolve any queries of the data, check for serious adverse events, and answer questions on the study conduct. During these visits, the CRA will also check the dispensing log to ensure the correct supplies have been dispensed at each visit, check the log of returned medications, and assist with the reorder of additional supplies or disposal of returned or unused medication.
g. Study Follow-up	- As the database is finalized, the company will generally contact the site to resolve queries.
h. Database Resolution	- Once the database is as clear as possible, decisions will be made as to which patients are "evaluable by protocol."
i. Analysis	- A full statistical analysis of the efficacy and safety data, usually using an Intention-to-Treat (ITT) analysis of all patients randomized the therapy, and a "per-protocol" analysis of only those patients who entered the study according to the current inclusion/exclusion criteria, and complete the phases of the study according to protocol.

j. Report Writing	- All the issues, results, and analyses are displayed in a report that concisely summarizes the study. Complex studies with many primary and secondary parameters may have multiple analyses such that a complete report (including a summary of all the dispensing and compliance records) may be 2000 to 5000 pages long.
k. Publication	- From a very detailed report of all the parameters, problems, assumptions, and analyses, a relatively short publication will be prepared. Within the company, the appropriate study manager will be aware of all the vagaries of the study, as the regulatory authorities will certainly question details to a much greater extent than any journal editor or referee.

Please bear in mind that entire books are written on these subjects; the intent of this summary is to indicate that a study initiated by a pharmaceutical company is not the result of an investigator and a statistician agreeing a brief design. Rather, it involves many disciplines, even more people, and will be conducted to GCP, and meet local regulatory requirements. All the problems, deviations, and other horrors will be detailed and explained in the research report. I am always reminded of this when new physicians join the industry; they are not used to such bureaucratic detail in academic research and publication, but then their previous studies were not necessarily conducted under regulatory requirements. The pharmaceutical industry is a regulated industry, and no compromises can be accommodated.

X. THE ROLE OF THE HOSPITAL PHARMACIST IN A CLINICAL STUDY

Unfortunately, the hospital pharmacist is often involved late in the site selection. Ideally, the CRA should meet with the pharmacist and investigator together, and ensure that all details are understood and dispensing instructions agreed. When the study starts, the clinical supplies are provided with a detailed dispensing log. This must be completed to record the details of all supplies dispensed and record what supplies are returned. Because supplies are usually prepackaged for every patient, with a separate package detailed by patient number, visit number, etc; the physical volume of such supplies can be large. Companies are on occasion challenged by hospital pharmacists questioning the sheer size of the supplies provided, but it is because of the complexity of some studies, the potential for different doses (therefore, multiple supplies per patient need to be supplied), and the need to have separate packs for each visit, that the packaging is a major logistic undertaking in itself. All companies appreci-

ate the value of the pharmacist in ensuring that clinical trial supplies are appropriately stored, dispensed, recorded, and destroyed, even though this is an additional burden when compared to dispensing an approved drug.

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Formulations Used in Clinical Trials and Their Bioequivalency to Marketed Product

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I. INTRODUCTION

It would be attractive to believe that clinical trials materials could always be developed such that they were identical, both in formulation and processing factors, to the product that ultimately reaches the market. Unfortunately, this is rarely the case.

For most pharmaceutical products, the materials used in clinical trials will show one or more significant differences from the marketed product. It is not surprising, therefore, that regulatory authorities in many countries direct scrutiny to the evidence produced by the sponsor of a new product that bio-

equivalence exists between the clinical trials material and product to be marketed.

II. REASONS FOR CONCERN ABOUT BIOEQUIVALENCE

The literature is replete with reliable references that clearly demonstrate that both the rate and extent of drug absorption can be substantially modified by formulation and processing variables (1). Thus, if there is any significant change in the formulation or process during the clinical trials development period, the question of bioequivalence will need to be addressed. If a marketed product is not bioequivalent to the clinical trials material, the possibility exists of hypotherapeutic or hypertherapeutic blood levels of drug occurring with the marketed product. This could result in either inadequate responses in patients or alternatively in an unacceptably high and unnecessary increase in the incidence of advance drug reactions. Thus, the need for some type of bioequivalency test for clinical trials materials and marketed product is quite obvious. What is less obvious is the number of tests that may be necessary and the protocol that should be used. The topic of bioequivalence, as it pertains to generic products entering the market and deemed to be therapeutically equivalent with the innovator's product and other generic versions of the same drug product already on the market, has received extensive attention from both pharmaceutical scientists and regulators. Although some aspects of such tests may still need additional modification, there does appear to be, at least in North America and the European Union, a broad general concensus of the essential principles to be applied in the design, execution, and interpretation of bioequivalency tests for generic products. Indeed, in some jurisdictions, regulatory bodies will provide "cookbook" recipes for bioequivalency tests for a number of specific drug products. These protocols contain information on such important issues as the recommended number of subjects, sampling times, and number of molecular species to be quantified. The author is unaware of any official document that provides similar guidance for bioequivalency studies needed as an essential part of the process whereby new chemical entity (NCE) is taken from the laboratory to the marketplace.

It is tempting to assume, either explicitly or implicitly, that we can apply generic equivalence type procedures to clinical trials bioequivalence studies without any modification. On reflection, however, there are significant differences in the objectives of the two types of bioequivalency studies, and these differences may legitimately be used to justify differences in standards for protocol design and study interpretation. In a recent publication (2), I used the term *development bioequivalency* for the study in which a clinical trails material is compared to the final marketed product. In contrast, the term *generic bio-*

equivalency was applied to the more well-known tests, the purpose of which is to provide assurance of equivalent prescribability or interchangeability of generic and innovator's product in clinical use by individual patients. In contrast, the purpose of a development bioequivalency study is simply to build a bridge between a product used in clinical trials with a version that will actually be marketed.

III. DEFINITION OF DEVELOPMENT BIOEQUIVALENCE

As indicated in the previous section, it is important to appreciate that development and generic bioequivalence, although similar, are not identical. Thus, it is useful to try to define, with some precision, what is meant by development bioequivalence. Perhaps it is appropriate to define development bioequivalence tests as being acceptable if they result in the accumulation of scientifically reliable data that prove that the rate and extent of drug absorption for materials used in clinical trials are essentially the same as for the marketed product. The determination of what is meant by "essentially the same" may depend on the pharmacokinetic and pharmacodynamic properties of the individual drug substance. Thus, the type of blanket definition of bioequivalence as is often given for generic drug products (i.e., 80% to 125% for the ratio of area under the curve AUC, T_{max} and C_{max}) may be too simplistic for development bioequivalence. (In fact, this type of definition may well need modification for generic bioequivalence, with the acceptable ranges being adjusted in accordance with the properties of individual drug substances. However, political and scientific factors are likely to retard this development for generic equivalence. In contrast, as is pointed out later, the potential for such modification for development bioequivalence testing is much brighter.)

IV. DESIGN OF DEVELOPMENT BIOEQUIVALENCY TESTS

It seems eminently reasonable that if the sponsor of the regulatory document (such as in DAN) submitted for the marketing approval of an NCE chooses to comply with the relevant standards accepted by the appropriate regulatory agency for generic bioequivalence, then such data should be regarded as fully satisfactory. For example, a test with a statistical power of 80% with respect to a 20% difference in the three key pharmacokinetic parameters AUC, T_{MAX}, and C_{MAX} should be accepted without question as being of a satisfactory design unless there are some most extraordinary circumstances. However, I believe there are occasions when other type tests may be equally, if not more, appropriate for development bioequivalence.

A. How Many Development Bioequivalence Tests Are Needed?

The simplest case in consideration of development bioequivalence occurs when the clinical trials formulation is identical to the formulation selected for the marketed product. In such a happy, but not common, circumstance, there is no need for any developments bioequivalence study per se, although many regulatory authorities may well require some information on the absolute bioavailability of the drug substance in the marketed product as may be obtained by a comparison of plasma concentration/time profiles of the product to be marketed and intravenous injection of the drug substance.

The next simplest case exists when one formulation has been used in clinical trials, and one separate formulation is selected for the product to be marketed. In this instance, one development bioequivalency text will be needed.

Suppose that two separate formations have been used in clinical trials, C1 and C2, and both are significantly different from the product to be marketed, M. If two separate development bioequivalency tests are performed and it is demonstrated that C1 = C 2 and C2 = M, then the argument has been advanced that development bioequivalency has been adequately demonstrated. The obvious weakness in this argument is that since C1 has never been directly compared with M, it could quite possibly be bioinequivalent to M because of the tolerances, specified previously, for the definition of bioequivalence. Therefore, in such a case it is preferable to conduct a three leg development bioequivalency study in which both C1 and C2 are directly compared to M. Obviously, the more legs we add to such a study, the greater the possibility of one or more pharmacokinetic parameter not being acceptable.

In fact, it is quite possible that a rigorous evaluation of all the manufacturing processes and formulation components used in an extensive program of clinical trials may well reveal that three or more development bioequivalency tests would be needed. The imagination boggles at such a prospect! Although I am not aware of any written, official pronouncements by regulators from agencies, such as FDA, I am aware of instances in which individual officials have been very reasonable in appreciating the difficulties presented by this type of situation. However, as is pointed out in section V, it is prudent for the sponsor of an NDA or comparable document to take all reasonable steps to avoid this problem.

B. What Should Be Measured?

The most obvious species to quantify is the drug substance per se, normally in plasma or blood using some appropriate physicochemical method, such as high-performance liquid chromatography (HPLC), for qualification. However, whereas for conventional, micromolecular drugs presently available, analytical

techniques usually allow such determination without difficulty, those of us dealing with polypeptides or proteins may have difficulty in developing an appropriate physicochemical analytical technique of acceptable precision and sensitivity.

Is it essential to quantify metabolites as part of a development bioequivalency test? There is no clearly articulated official policy. Certainly if the metabolites are not pharmacologically active, such work is not required even for a generic bioequivalency study, and there is even less justification for a requirement of metabolite quantification in a development bioequivalency test. The argument put forward in generic bioequivalency in favor of quantifying active metabolites is that since such studies are performed to provide assurance of therapeutic equivalence, it must be mandatory to quantify active metabolites. Since in development bioequivalency our aim is simply to demonstrate that the drug product to be marketed has essentially the same in vivo release characteristics, there would seem to be no justification for normally requiring quantification of any metabolite, whether active or inactive. The only exception would be if the drug were converted so rapidly to the metabolite as to make its quantification, with an acceptable degree of precision, impossible.

In some instances, quantification of the drug by physicochemical techniques such as HPLC may not be feasible. In these cases, some type of in vitro bioassay (e.g., clot lysis for tissue plasminogen activator [TPA]) may be appropriate.

Whenever possible the study should be conducted using single-dose crossover design. However, for drugs with a long half-life, this may not be possible, and a parallel design may have to be used. Although it is desirable to measure plasma concentration so that AUC equals AUC infinity, this is not necessarily essential and even truncated AUC values can provide a reasonable basis for estimating bioequivalence (3,4).

C. What Standards Should Be Used in Evaluating Results?

For generic bioequivalency studies, some regulatory agencies direct attention not only to average data but also to the variability individual subjects may show when receiving the two treatments. In the past, for example, FDA used the 75/75 as a method of determining whether intrasubject variability was acceptable. This rule was not based on any accepted statistical theory, but was an attempt to develop an empirical test that would be of value in definitions therapeutic equivalence *as would be experienced by individual patients*. Since in evaluating development bioequivalence we are only planning to market one version of our product, the question of variability in individual subjects is not relevant, and thus there would seem to be no valid reason for giving any attention to this parameter in development bioequivalence studies.

The statistical power of the test and the acceptable ranges for a determination of development bioequivalence are areas in which we may implicitly assume that standards used in generic bioequivalency will also be applicable in development bioequivalency. I would argue that such an assumption is not necessarily valid. It is widely accepted by regulatory agencies that a 20% range for both average and confidence bounds is reasonable for the definition of bioequivalency with respect to AUC, C_{MAX}, and T_{MAX}. Although this standard appears to have worked reasonably well, there is no theoretical basis or body of reliable quantitative, clinical data to support this limit. On careful analysis, we are forced to admit that the selection of a 20% range for acceptability is essentially arbitrary. It is hard to accept that there really is any justification for imposing a uniform standard for bioequivalency limits for all drugs regardless of their individual properties. For drugs with a very shallow dose response curve, it may well be that limits of 50% may be acceptable. By contrast, drugs with a steep dose response curve might well require a tighter specification, possibly 10%. Although this principle may be generally recognized, it has been difficult to apply it in practice for generic bioequivalency tests.

Unfortunately, in decisions concerning standards for generic bioequivalency, political as well as scientific factors are involved. If a regulatory agency relaxes standards for bioequivalency, it is quite possible that the company that originally developed the drug substance may take action, such as filing a citizen's petition, to prevent the agency from implementing such a policy. It is quite natural for the research-based company to be defensive about the competition generic products will pose. However, it is difficult to accept that all such defensive actions are scientifically justified or in the best interests of the public.

Information about essential pharmacologic data such as the slope of the dose-response curve for an individual drug is not always available in the public domain. Thus, generic pharmaceutical companies seeking the approval of a regulatory agency for the relaxation of the 20% limits for generic bioequivalency determination are at a distinct disadvantage. Also, for many drugs, there is a distinct paucity of reliable published data on the variability of acceptable therapeutic blood levels determined from patients using the drug in normal clinical practice. In the absence of such data, it is not easy to develop a convincing case to persuade regulatory agencies that a limit of other than 20% should be used for the definition of generic bioequivalency.

During the process of the development of a new chemical entity, the sponsor may obtain pharmacokinetic and pharmacodynamic data that impinge directly of the appropriate rational limit for bioequivalence (Tables 1 and 2). It is to be hoped that sponsors may be willing to present such information to regulatory agencies so that development bioequivalency limits can be based on reliable data pertinent to the individual drug substance being developed.

TABLE 1 Number of In Vivo-In Vitro Correlations Found Among the Total Number Investigated

Drug	Type of parameters evaluated	Number of ANDAs evaluated	Total number of correlations evaluated	Number of correlations
Diazepam	All	16	96	2
	Test/reference		72	3
Doxepin HCl	All	16	18	0
Ibuprofen	All	50	54	2
	Test/reference		54	3
Lorazepam	All	17	54	2
Total	Test/reference		54	6
		99	402	18

Source: From ref. 4

TABLE 2 Pharmacokinetic Studies: Phase I–III

Study	Clinical phase	Objective	Suggested design	Comments
Pilot pharmacokinetic (single- and multiple-dosage)	I	Validation of analytical method; preliminary pharmacokinetics	Parallel groups (n = 3 - 6/group); suspension or solution dosage form if possible; minimal number (6/subject) of blood samples collected	Normally part of single- and/or multiple-dosage safety and tolerance studies
Pilot bioavailability	I	Pilot study to determine if solid dosage form adequate for phase II and III studies	Single-dosage crossover (n = 6–12); solution or suspension vs. solid dosage form	
Single-dosage ADME	I	Obtain definitive pharmacokinetic data, excretion pattern, dosage proportionality, definitive metabolism; project pharmacokinetic parameters for multiple dosing	Single-dosage parallel groups (6/group); radiolabeled drug in solution or suspension at two dosage levels; urine and feces as well as serial blood samples collected	
Intrasubject and intersubject variability	II	Determine variability expected during phase III pharmacokinetic studies and determine number of subjects required in future pharmacokinetic studies to assess differences adequately (statistically)	Three-way crossover (n = 12) using same dosage solution or suspension (dosages one-half highest tolerated dosage)	
Dose proportionality	II	Determine if bioavailability parameters (C_{max}, AUC) are linear over proposed dosage range	Three-way crossover (n = 12); solution or suspension covering the therapeutic range for a single dosage	

Dosage proportionality	II	Determine if bioavailability parameters (C_{max}, AUC) are linear over proposed dosage range	Three-way crossover (n = 12); solution or suspension covering the therapeutic range for a single dosage	
Multiple-dosage ADME	II	Validate single-dosage pharmacokinetic projections; determine ADME profile on multiple dosing; obtain large quantities of biological fluids for biotransformation studies	Single daily dose of radiolabeled drug in solution or suspension for 4–5 days in 6 subjects; C_{min} values obtained during dosing and complete blood profile after last dose; urine and feces collected during entire study	
Bioequivalence of service and proposed marketed dosage forms	III	Determine if dosage form(s) using during clinical trials is (are) bioequivalent to dosage form proposed for marketing; determine relative bioavailabilities of service and proposed market forms	Single-dosage crossover (n based on results of dosage proportionality and/or variability study using power calculation); highest strength dosage form proposed for market should be evaluated	Pivotal study for registration
Dosage form proportionaligy	III	Determine if equipotent drug treatments administered as different dosage strengths of one dosage form produce equivalent drug bioavailability	Single-dosage crossover (n based on dose proportionality, variability, or prior bioequivalence studies); multiple strengths evaluated by bracketing (i.e., using lowest and highest dosage strengths for study)	

(*continued*)

TABLE 2 Continued

Study	Clinical phase	Objective	Suggested design	Comments
Food interaction	III	Influence of food on bioavailability	Single-dosage crossover (n = 9–12); dosage form proposed for marketing should be used if available	
Effect of age	III	Influence of age on pharmacokinetic parameters	Single dosage in elderly volunteers (n = 25)	Results compared to those obtained from other pharmacokinetic studies using younger volunteers under the same experimental conditions
Renal insufficiency	III	Influence of renal function on pharmacokinetic parameters	Single dosage in patients (n = 12) with creatinine clearance <25 ml/min	Results compared to those obtained from other pharmacokinetic studies using subjects with normal renal function under similar experimental conditions; study not essential if renal excretion of drug and/or metabolites minimal
Hepatic insufficiency	III	Influence of hepatic function in pharmacokinetic parameters	Single dosage in patients (n = 12) with confirmed hepatic insufficiency	Results compared to other pharmacokinetic studies using subjects with normal hepatic function under the same experimental conditions
Drug–drug interactions	III	Influence of concomitant medication on bioavailability parameters	Single-dosage three-way crossover (n = 12–18); comparison is drug plus codrug, drug, codrug	Choice of codrug based on preclinical data, experience with other drugs, likely comedications

V. STRATEGIES TO REDUCE BIOEQUIVALENCY PROBLEMS WITH CLINICAL TRIALS MATERIALS

Probably the most important elements is any strategic plan for which the objective is to minimize development bioequivalency problems are coordination and control. There should be coordination between all involved in the formulation and processing of clinical trials to ensure that, wherever possible, there is uniformity of the materials used at all clinical sites and appropriate quality control tests applied to all such materials. Of course, this objective is not always easy to attain. When a large number of clinical trial sites are used and the clinical trials are continued over a significant time, there is a natural centripetal tendency toward diversity that must be resisted. There is, therefore, a powerful argument in support of the practice used by some companies of charging one person or a small committee with responsibility for monitoring the development of all clinical trial material for any given drug.

There is also advantage to following the practice used by some pharmaceutical companies of trying to use a "boiler plate" standard formulation for all conventional (micromolecular) drugs administered by the oral route. This simple, rugged, type of formulation can be applied in many parts of the world using widely available simple production equipment.

Even if these strategies are adopted, there may be occasions when a sponsor will be faced with the unpleasant reality that four separate formulations have been used (or are being used) in clinical trials. The cost of a five-leg bio study is, of course, very substantial and the chance that one or more of the formulations may fail bioequivalence requirements on one parameter is significant. Obviously, therefore, we would wish to avoid such a test if possible. In such circumstances, there may be a temptation to postpone addressing the problem. Perhaps it may be hoped that if it is hidden well within the interstices of a complete NDA, it may be overworked. This approach may sometimes be successful. However, it is probably much better most of the time to address the problem fully and honestly as early as possible. A meeting with officials of the regulatory agency may be fruitful in such instances.

When a meeting is requested with staff of a regulatory agency such as FDA to discuss a possible problem with a development bioequivalence issue (or for that matter with any aspect of clinical trials), it is important to plan and execute the meeting carefully. It is not a good idea to acquire a reputation at FDA as being a company that is always bothering the agency with requests for meetings. Thus, it may be appropriate to place several related items on the agenda for a meeting.

In preparing for the meeting, rational arguments as to why not all clinical trials material should have to be subjected to a development bioequivalency study should be developed. Is there one clinical trials formulation that was only

TABLE 3 Allowable Range of Noncritical Components (Percentage of Total Formula)

Noncritical component	% of total formula
Filter	5
Disintegrant	
Starch	3
Other	1
Binder	0.5
Lubricant	
Ca or Mg stearate	0.25
Other	1
Glidant	
Talc	1
Other	0.1
Film coat	1

used to a very limited extent? Are the differences between two of the clinical trials formulation so small that it might well be reasonable to use in vitro tests such as dissolution to monitor comparability rather than using a bioequivalency test? It must be appreciated that in vitro/in vivo correlations cannot be assumed. Remember that FDA does allow some variation in "noncritical components" (Tables 3 and 4).

TABLE 4 Typical Pharmacokinetic and Metabolism Studies Conducted During Full-Scale Clinical Development

Single-dose pharmacokinetics
Multiple-dose pharmacokinetics
Metabolism
Additional fed–fasting studies
Enzyme induction
Mass balance
Formulation bioavailability
Pharmacokinetics comparison with competitive products
Special populations, renal, liver disease
Elderly vs. young
Drug–drug interactions
Continued toxicology monitoring and toxicokinetics, long-term toxicology
Therapeutic drug monitoring
Population pharmacokinetics
Pharmacokinetic–pharmacodynamic relationships
Bioavailability/bioequivalence of market image dosage form
Regulatory summary documents

TABLE 5 Rhodes' Three Laws of Meetings at FDA

The First Law

$n_1 < n_2$

Where n_1 is the number of people attending the meeting from the sponsor and n_2 is the number of people attending from FDA.

The Second Law

$P = K/(n_1 + n_2)$

Where p is the progress made at the meeting and K is the meeting constant.

The Third Law

$P \rightarrow O$ Esq.

Where *Esq.* indicates the presence of a lawyer at a meeting focused on scientific or clinical, rather than legal issues.

Table 5 summarizes Rhodes' three laws of FDA meetings. As can be seen from this table, I am an advocate of limiting the numbers of persons attending the meeting. For meetings on scientific or clinical subjects, I generally prefer to avoid the use of lawyers.

Who should attend a meeting at FDA? I am a strong believer in using the scientific or scientific staff of the sponsor to meet with FDA personnel rather than simply relying on persons from the company's regulatory affairs department. After the meeting, it is useful to send a letter to FDA summarizing the sponsor's understanding of what transpired at the meeting. This can help prevent misunderstanding.

It is essential that the material designated as marketed batch shall indeed fully justify that designation. Thus, it should be manufactured on production equipment with a batch size comparable to that used in production. For compressed tablets, this would usually involve a batch of at least 100,000 tablets.

VI. SUMMARY

The primary theme underlying this chapter is that it is unrealistically simplistic to assume that development bioequivalency is, or should be always, the same as generic bioequivalency. Sponsors of NDAs, or comparable documents in non-U.S. jurisdictions, should monitor clinical trials carefully with a view to reducing development bioequivalency tests as far as possible. There is a case for regulatory agencies providing more written guidance in this area than is presently available.

ACKNOWLEDGMENTS

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5

Drug Substance Development Issues in the Control and Production of Clinical Supplies

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I. INTRODUCTION

The first stop in the development pathway of a new chemical entity (NCE) is the Department of Chemical Development. Supplies of the NCE are necessary to begin initial chemical and physical evaluation, drug safety studies, dosage form preparation, and other activities that are necessary for the filing of an Investigational New Drug (IND) application with the Food and Drug Administration (FDA).

*Retired

In general the mission of a chemical development department is to ensure the timely availability of NCEs for use by other departments and, ultimately, to develop safe, efficient, and environmentally neutral processes for their manufacture in a production plant. There is a great deal of variation in the internal organization of a chemical development department and its place in the overall organization within a pharmaceutical company. The department itself is generally made up of two main groups: a process research unit, whose main function is the discovery, development and optimization of a process on a laboratory scale and a scale-up unit, whose function includes (a) the development and definition of the technical and operational parameters of the process, (b) their optimization on a larger scale, and (c) the eventual transfer of this information to a chemical production unit.

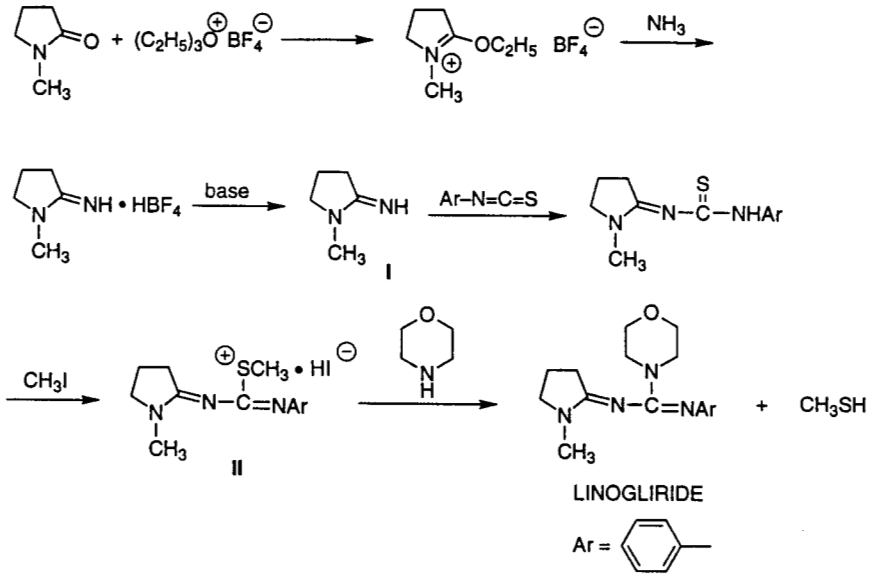
Some pharmaceutical companies have their own chemical production plant for the preparation of drug substances on a commercial scale. Others choose to use outside custom manufacturers for this function. In the former case, a separate chemical development unit may be associated with the production plant.

In both cases, the transfer of the technology for the preparation of these new NCEs presents a challenge. The process is always easier when the manufacturing plant is part of the overall organization of the same company. In the case of using custom "outside" manufacturing companies, the transfer process becomes lengthier and more tedious. Some aspects of this type of transfer are discussed later.

II. MEDICINAL CHEMISTRY TO CHEMICAL DEVELOPMENT

A medicinal chemist's primary goal is to synthesize target molecules chosen for their potential for useful biological activity. The safety or efficiency of the synthesis is not a primary consideration. A well-designed synthetic strategy, for the medicinal chemist, will produce the largest number of compounds (analogs) in the shortest time. An example, taken from our files, is shown in Scheme 1; we will follow the development of the synthesis in this example as we discuss activities from the medicinal chemistry laboratory to chemical production.

This route was designed to give the medicinal chemist maximum flexibility in varying the group Ar (a substituted or unsubstituted aromatic ring) and the central amine (in this case morpholine), thus producing a variety of analogs from the common intermediates I and II. The six-step process shown in Fig. 1 was not a practical large scale method, primarily because of the use of triethyloxonium fluoroborate in diethyl ether and the evolution of methyl mercaptan, a noxious and foul-smelling gas. This process was used initially for the preparation of the drug substance linogliride and its salts. Later it became the job of the development chemist to improve and optimize this original process or to discover a new one. The first activity for a development chemist is the preparation of a sample of the new compound, following the original medici-



Scheme 1

nal chemistry synthesis. An evaluation is made at this time about the safety of the process, as well as its operability (e.g., volume vs. output, purification techniques, etc.) and the availability and cost of the raw materials and reagents used. Often, the medicinal chemistry route is adapted, with minor modifications, for the synthesis of up to 1 kg of the drug substance. Sometimes alternate methods for the preparation of an intermediate must be defined. On rare occasions, a completely new synthesis is necessary to produce the required early developmental quantities of the NCE.

It is important at this stage of a project to produce needed supplies as quickly as possible so as to be able to begin prephase I studies. A final optimal process can be developed later, after the NCE has been shown to be safe (phase I) and effective (phase II).

A. Preparation of Salts

A number of biologically acceptable salts of a basic or acidic NCE are prepared to produce a compound with the best physical characteristics. The evaluation of the salts is carried out by a preformulation laboratory, usually a part of the formulations department. The bioavailability of some of the salts (animal studies) may also be evaluated to aid in the selection of a salt. In the case of our example, linogliride, several organic and inorganic acid salts were prepared. Criteria for the final choice included dissolution, intrinsic solubility, compatibility and interactions with excipients, and stability, both in terms of degra-

dation and hygroscopicity. The formation of polymorphs is also investigated at this time. Polymorphs are different crystals habits of a compound. Their formation may be dependent on the solvent or mixtures of solvents used during the crystallization process, the concentration of the solution, the rate of cooling, or other factors. Polymorphs usually exhibit different physical properties, including melting points, infrared spectra, dissolution (and therefore bioavailability), and stability. Control of formation of a single polymorph is sometimes difficult and, in rare cases, impossible. The best that can be achieved in these circumstances is the preparation of a constant, reproducible mixture of polymorphs.

At the same time, an analytical evaluation of the new compound begins. This involves development of analytical methods for an assay of the compound itself and for the determination of the number and amounts of impurities present. The development of these methods will generally be preceded by discussions between scientists from Chemical Development and Analytical R&D. The synthetic pathway is reviewed, and possible and probable by-products or degradation products are outlined. The analytical method used is generally high-performance liquid chromatography (HPLC) and is tailored to detect and separate probable impurities from the main product. It is usually the responsibility of Chemical Development to provide samples of these impurities as authentic analytical reference materials. The purity of these materials is generally >95%. These samples are used primarily for the verification of the identity of the observed impurities. Other parameters that are investigated include water content, residual solvents, heavy metals, residue on ignition, and others, as appropriate for the particular compound in question. Most companies set a purity limit of not less than 98% for the compound under study and not more than 0.5% for individual impurities. A weight-percent HPLC assay, using a working standard sample, is used to determine the purity of the drug substance and the level of the impurities. The limits for the latter or for a single specific impurity or by-product may be higher, depending on the complexity of the synthetic or purification methods used at this stage of development. Some examples may include enantiomeric or diastereomeric impurities and fermentation or peptide by-products. Procedures and guidelines used for the choice of final specifications are presented in the section Optimization.

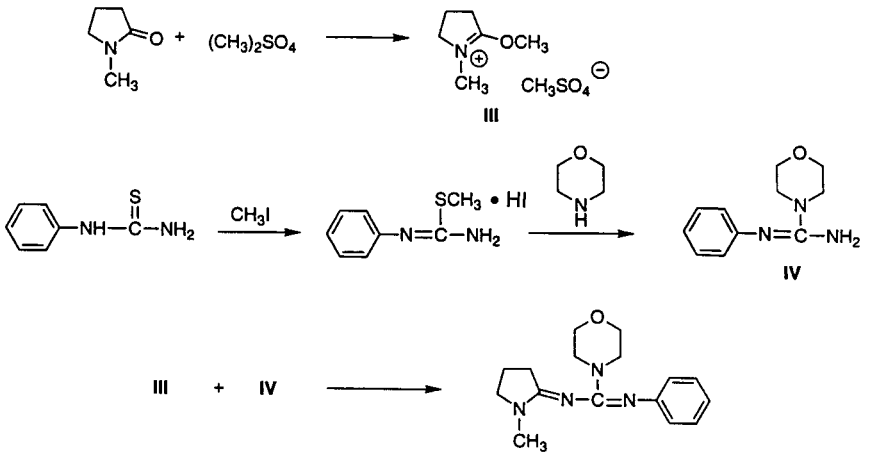
B. Process Definition

At this point, a method of synthesis for the preparation of preclinical supplies has been defined, an appropriate salt has been chosen, and an analytical method has been developed. Let us assume that the project is moving ahead. The next task for Chemical Development is to provide NCE for further developmental work. Supplies are needed for the development of formulations, drug safety,

and clinical studies. From initial analysis we already have an idea whether the synthesis used for the preparation of the NCE is suitable for further scale-up. In addition to the necessity of, and the primary concern for the immediate continuation of supply, we now begin to take a longer range view: Is the current synthetic route viable for projected commercial production (sometimes many metric tons)? If so, what aspects of the synthesis need to be improved? If not, what are alternate methods and which of these alternates should be pursued? This type of analysis has far-reaching implications; long-term toxicity studies will probably begin sometime toward the middle of phase II. The synthesis method chosen will, in effect, "fix" the impurity profile of the drug substance. Significant changes in synthesis, different raw materials, or even new reagents may introduce new impurities in the final product, necessitating the identification of new impurities and the repetition of some drug safety, bioavailability or, in some rare cases, clinical studies.

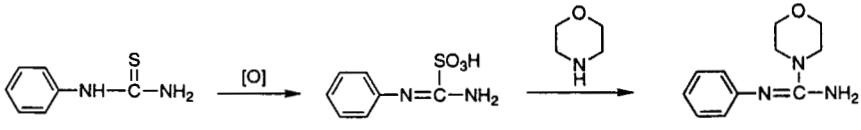
For linogliride, it was clear that for the preparation of multikilogram quantities, the use of triethyloxonium fluoroborate and ether would have to be eliminated. The following alternate scheme was devised (Scheme 2). The N-methyl pyrrolidinone was activated using methyl sulfate. The order of attachment of the various units of the final molecule was changed.

This route still has the liability of evolution of methyl mercaptan; this was considered to be manageable for this stage of development and for the amounts of drug substance required. This process was indeed scaled up in the pilot plant to produce upwards of 100 kg of product. Methyl mercaptan was contained by absorption into a solution of caustic, followed by oxidation to nontoxic sulfate



Scheme 2

compounds. Nevertheless, a process that involved methyl mercaptan was considered unsuitable for the long-term production of a bulk pharmaceutical. Alternatives to the activation of the C-S bond in arylthiourea, for displacement with an amine, were sought. After much research, the following, eventually patented, process was developed for the preparation of the intermediate IV (Scheme 3).



IV

Scheme 3

Compound IV was converted to linogliride as before. This particular approach achieved activation of the sulfur through a simple oxidation process, resulting in displacement by-products that were water soluble, environmentally acceptable sulfates. We were thus convinced that this was to be the eventual commercial route to linogliride. Unfortunately, the clinical program was not entirely successful, and development of this compound was discontinued.

A second, somewhat different example of the progression from early processes to the eventual manufacturing method involves the synthesis of peptides. Most, if not all, new synthetic peptides are prepared by the so-called solid-phase peptide synthesis (SPPS) method. This procedure (the Merryfield method) involves attachment of one amino acid (AA) to an insoluble resin, followed by the sequential coupling of this AA to the rest of the AAs making up the peptide.

Let us consider a 10 AA peptide as an example: AA_1 - AA_2 - AA_3, — AA_9 - AA_{10}. In SPPS, AA_1 would be attached by a covalent bond to a resin; AA_2 will be coupled to AA_1, the free end deprotected, activated and reacted with AA_3. This process is repeated until all AAs are attached. The peptide is then removed from the resin, may undergo further chemical manipulation, and is purified, often by preparative HPLC, followed by lyophilization. This method, depending on the nature of the peptide, is suitable for the preparation of from hundreds of grams to several kilograms of product.

It is limited in size because of the physical manipulation required and the very large amounts of solvents necessary in each coupling step. If larger quantities are required for marketing a more conventional liquid-phase peptide synthesis (LPPS) should be developed. Normally, small peptide fragments will be synthesized, e.g. AA_1 - AA_2 - AA_3 and AA_4 - AA_5 - AA_6 - AA_7 and AA_8 - AA_9 - AA_{10} (A 3-4-3 breakup), and then fragments will be coupled to produce the desired peptide. Alternatively, one may consider different breakups, e.g., 2-4-4- or 4-2-4- or 2-6-2-, etc. Considerable research and time are

needed to define the coupling strategy and to optimize the synthesis of the fragments themselves. While it is expedient to initiate development work using SPPS, a decision to proceed to LPPS and to initiate studies to arrive at a workable synthesis must take place, as early as possible. The development of an LPPS may take considerable time, sometimes years, depending on the length of the peptide and the nature of the amino acids present.

A further issue that has gained prominence during the last 5 years is the guideline to develop single isomers of compounds containing one or more stereogenic centers.

For the sake of simplicity and ease of illustration, let us consider an investigational drug with one stereogenic center; this compound would exist as a racemate, i.e., two enantiomers. The biological activity may be due to one enantiomer, while the other may be inactive or even have some undesirable pharmacology or toxicity. Both enantiomers have to be prepared, in pure form, to investigate their properties. Should the activity indeed reside in only one isomer, this isomer has to be prepared in enantiomerically pure form, while its enantiomer will be considered a by-product or an impurity. A strategy for the preparation of a single enantiomer needs to be set. There are four general ways to obtain pure isomers: (a) physical separation of a racemate through the formation of disatereomers, (b) preparative chiral chromatography, (c) enzymatic separation, generally of an intermediate racemate, and (d) asymmetric synthesis.

The fastest way to obtain material for testing is the classical, physical separation method (item 1). As in the case for SPPS for peptides, this method involves many manipulations and is, generally, not amenable to large scale operation. There are always exceptions, and a separation strategy should not be discarded without thorough consideration; asymmetric synthesis, either in toto or from enantiomerically pure intermediates may be the best choice for commercial manufacture. Development and optimization of these methods is time- and manpower consuming, not only for the synthetic aspects, but also for the identification of analytical methodology. Work should start as early in the project timeline as possible.

In the last 3 to 4 years, new approaches in the drug discovery process have necessitated changes in the traditional modus operandi during the preclinical and early clinical stages of development. Computer and robotics-assisted pharmacological testing (high throughput screening with very small amounts of material) and synthesis (combinatorial chemistry) have increased the number of compounds available for testing by an order of magnitude. Libraries of compounds (thousands to tens of thousands) have become available to the pharmaceutical industry for rapid evaluation of biological activity. Promising drug candidates are identified for clinical testing. The increased number of com-

pounds tested leads to an increased number of compounds with interesting activity.

It is impossible to test each of these in the clinic, in the traditional manner previously discussed in this chapter; the resource requirements would be prohibitive. Instead, one uses a different strategy to test the safety and efficacy of these compounds in humans. This strategy generally involves the preparation of one small lot of drug substance to be used in a reduced preclinical program to support a very limited, specific clinical trial. The medicinal chemistry route of synthesis is used without regard to future scale-ups or process development, to produce this one lot. Analytical and formulation work is kept to a minimum. A clinical marker is defined to assess the activity/efficacy in humans (e.g., reduction/elevation of an enzyme or hormone). The consequence of this strategy is that, in early developmental stages, the development chemist is faced with synthesizing many compounds on a smaller scale rather than a few compounds on a larger scale. Care, of course, must be taken in the preparation of these compounds to follow good manufacturing practices (GMP), since they will be used in clinical trials. It may also be necessary to make changes in existing facilities to implement this approach. Classical pilot plants (or a part of them) with process equipment in the range of 200 to 500 liters may be modified to eliminate a number of reactors and replace them with a larger number of smaller vessels (50–100 liters). It may also be necessary to separate these vessels in cubicles to avoid cross-contamination during the simultaneous operation of multiple projects. If a compound is deemed sufficiently interesting for full development to an NDA, then more stepwise, classical approaches, described earlier, must be adopted.

Even with the comfort level of a limited positive clinical trial, it is difficult to decide when to begin extensive and detailed process work, for the definition of the final manufacturing method. The attrition rate of compounds at this stage is probably greater than 60%. Obviously, this means that more than half of the compounds for which significant process work has been carried out, will never become commercial products. In other words, half the work that a process group carries out at any given time in the developmental timeline may be wasted! The case of linogliride, described previously, is one such example.

On the other hand, the FDA requires that the drug product used for the final validation studies of the formulation and for the all-important final bioavailability batch, be prepared using drug substance synthesized by the chemical method intended for commercial manufacture, at the actual manufacturing site, using production or near-production scale equipment. The drug product will then be subject to stability studies usually for 12 or more months. The data from this study are analyzed, reports written, audited by quality assurance and prepared for submission in an NDA. The real time period for

completing these activities is about 2 years. Retracing our steps, it can be seen that drug substance for these studies has to be available in early phase III.

Working further back in the development timeline, one can see that the final chemical process for the manufacture of the drug substance required for the validation work on the drug product has to be defined during phase II, to allow sufficient time for scale-up and the actual production of the validation lots.

These timelines are summarized as follows:

Process Definition	1–2 years
Scale-up	0.5 year
Validation Lot Preparation	0.4 year
Drug Product Stability	1.2 years
Document Preparation	0.6 year
Total	3.7–4.7 years

Many components and activities are associated with process work toward a final method. These include:

A. Choice of the actual synthetic route
B. Optimization
C. Process validation
D. Safety
E. Environmental concerns

The importance of these factors may vary depending on the compound under consideration. In the three examples (classical heterocycle, peptide, single isomer) discussed earlier, items A and B would be more critical in the case of the more complicated peptide and the single isomer than the case of simpler linogliride. For the latter, however, as discussed previously, environmental concerns were of paramount importance. Let us discuss the preceding items in some detail.

C. Choice of the Actual Synthetic Route

There are always several different ways to construct an organic molecule. Work starts with a review of the chemical literature. The information gathered is evaluated in the context of the work already carried out. One or two plausible routes are then chosen. These routes may be made up of many synthetic steps. One or more steps in the sequences may be a key in the success or failure of the overall method.

In our example of linogliride, the step involving the activation of sulfur, before displacement with an amine, is clearly critical to the successful elimi-

nation of methyl mercaptan. In the case of the peptide example, the efficient coupling of the fragments, without racemization, is the key.

Experimental work is usually carried out to examine and evaluate the difficulties and the amount of work that may be necessary to overcome these, and the final choice of the route depends on the results of such investigations.

D. Optimization

When it is established that a particular route fulfills the requirements set forth for the synthesis of the NCE, the development chemists begin a systematic, step-by-step optimization of all aspects of the synthesis. This optimization is carried out with support from analytical groups and with input from personnel from a production plant. In some cases, several parameters can affect the outcome of a reaction. It is possible to study the effect of each parameter by varying it, while holding other reaction conditions constant. However, in most cases, one parameter affects another, so that the simultaneous variation of all factors influencing the reaction may be useful. This can be accomplished by the use of statistical models (e.g., factorial design, simplex optimization).

In a factorial design, a matrix in which all parameters vary simultaneously (within some constraints) is created. The number of experiments within such a matrix depends on the number of parameters chosen. Results of these experiments are analyzed statistically; based on these, a new set of parameters may be set forth to fine-tune the reaction conditions further. Parameters included in such a study may be reaction time, temperature, concentration and rate of addition of one or more reactants, pH and others. The initial number of experiments necessary to reach optimum conditions may vary from 20 to 40.

A final process developed in the laboratory is then passed on to a scale-up group. This group could be made up of a large scale laboratory (sometimes called a kilo-lab) and a pilot plant made up of reaction vessels from 50 to 200 gallons. The new process is examined in detail by this group in terms of both chemistry and engineering. A technology transfer team is sometimes formed to ensure the complete and smooth dissemination of all the important information relating to the process. This team is made up of representatives of the laboratory and scale-up groups (both chemists and engineer(s)), from analytical and possibly from the eventual production site. This team will look at the reaction parameters from the point of safety, and environmental impact, as well as engineering aspects such as heat transfer, cooling curves, volume efficiency, and general operability.

At this stage of development, the process of setting the final specifications begins. The bases of this process are the International Conference on Harmonization (ICH) guidelines for both organic and inorganic impurities and residual solvents and the actual manufacturing experience of the drug substance, pre-

pared by the method of synthesis to be used for the commercial product. Those impurities that should be included in the specifications are referred to as "specified" impurities. Specified impurities may be identified or unidentified (referred to by relative retention time in the HPLC analysis) and are listed individually in the specifications. The rationale for listing individual impurities generally includes a discussion of the impurity profiles of drug substance lots used in safety and clinical studies, together with a consideration of the impurity profiles of material prepared by the proposed manufacturing method.

The industry standard is to include those impurities present in amounts greater than 0.1%. If new impurities are observed later, in a modified process or during scale-ups, they are "qualified" by carrying out appropriate (usually short-term) drug safety studies.

The group that makes the final recommendations or decisions for specifications includes representatives from chemical development (manufacturing experience), analytical development (methodology, assays), pharmaceutical development (dissolutions, micromization, particle size distribution), drug safety, QA, regulatory, and chemical production.

E. Safety

For any new chemical method, two equally important aspects of safety are considered: chemical and biological. Chemical safety involves an investigation of the thermal or other instability within the framework of the reaction conditions in each step of the synthesis. Differential scanning calorimetry (DSC) and reaction colorimetry (Mettler RC-1 calorimeter) are two of the most common techniques used to assess thermal instability; the self-decomposition temperature threshold of the individual raw materials and intermediates is examined, along with, in some cases, reaction mixtures themselves. In fact, in many cases, calorimetric measurements not only are useful in assessing safety, but provide valuable process information about the reaction being studied. The exotherms or endotherms observed may give clues about reaction initiation or completion or, in the case of crystallization, indication of the formation of polymorphs or mixtures of polymorphs.

If the normal operating temperature of a reaction is close to a thermal runaway (or self-decomposition) point, alternative reactions may have to be investigated or special safeguards may be engineered into the process.

Other safety testing techniques involve adiabatic reaction calorimetry (ARC), flammability, and dust explosions. The latter are important in drying or milling operations not only in the chemical plant, but also during formulation.

Biological safety involves exposure of the pilot plant staff to new compounds; the bulk drug itself has, of course, been tested in many drug safety tests

and thus its properties are well known. Little or no toxicological information is available for the intermediates used in the synthesis. Tests, therefore, are requested at this time generally involving an oral LD_{50} and general exposure irritation studies.

The safety information generated during development is reviewed with safety representatives of the manufacturing company; protective clothing, environmental monitoring, and worker education/exposure are some of the safeguards that may be necessary to avoid undue risks to operators.

F. Environmental Concerns

It is estimated that about one third of the cost of construction of a new plant, or addition to an existing plant for an NCE, is due to environmental factors. State and federal regulations require a complete analysis of all solid, liquid, and gaseous wastes associated with the production of an NCE. Special equipment is necessary in many cases to eliminate and discharge by-products of reactions, particularly if they involve certain metals used as catalysts.

Many synthetic procedures that would produce the desired compounds in high yields are not even considered because of environmental reasons. Some production plants have defined lists of reactions or techniques that are forbidden for their plants. Certain hydride reactions and reductions are immediately dropped from consideration; development groups will generally examine the synthesis route and rather than optimize or "engineer" the safety of a lithium aluminum hydride reduction, they will seek an alternate reduction method or will change the entire route of synthesis. Alternatively, the capital investment necessary to contain or safely remove certain residues or reagents may be too high to justify its use. The gradual elimination of the use of certain potentially toxic solvents has added to the constraints facing development chemists. They must be creative in devising methods that will be both technically efficient and environmentally benign.

One example is the use of tailor-made catalysts to carry out certain chemical transformations. Catalysts are used in small amounts, rather than in stoichiometric quantities, are generally completely recovered from the reaction mixture, and most times reused. Another example is to devise reagents and reaction conditions so as to carry out reactions in aqueous rather than organic solvent media.

Three kinds of wastes are generated in chemical plants, specialized in the production of bulk pharmaceuticals: gaseous, liquid, and solid wastes. Gases are generally absorbed in aqueous media, neutralized, as appropriate, and discharged through treatment plants. Liquid wastes may be aqueous (disposal plants) or organic; attempts are generally made to recover and reuse these

solvents; others are incinerated. Solid wastes are handled by licensed waste management companies.

III. CHEMICAL DEVELOPMENT TO CHEMICAL PRODUCTION

A. Technology Transfer

The information accumulated by laboratories and pilot plants should ultimately be transferred to a production plant. As seen in the timeline for development, this process takes place sometime during phase II. It is desirable to have phase III clinical supplies produced by the eventual commercial manufacturer of the NCE. This is important for two reasons: First, as discussed previously, the FDA requires that primary stability studies for both drug substance and product be carried out with materials prepared at the actual site and scale of commercial manufacture; timing for data accumulation and submissions coincide with the preparation of phase III supplies. Second, the impurity profile and physical characteristics of the drug substance can be best defined during the larger scale operations involved in the synthesis of phase III supplies.

A team is usually formed to oversee the proper and complete transfer of the technology from the development organization to the production unit. Many companies have a detailed protocol that outlines each step of this transfer, breaking down chemical, analytical, and engineering parameters and defining schedules, milestones, and feedbacks. After a few lots of drug substance are produced, data from the plant are analyzed relative to the efficiency of the process as performed on that site; this analysis include considerations of yield, safety, impurity profiles, and physical characteristics of the NCE. Sometimes the project is returned to the pilot plant for further workup, depending on problems observed in the plant. Either before the introduction to the plant or after the process is finally defined, a Hazards and Operability (HAZOP) review is carried out. The purpose of this review is to go over each step in the process and analyze every operation in detail, with respect to chemical and equipment parameters and to examine the consequences of either mechanical failures or operator errors. Special safety or backup systems may be put in place to overcome potential hazardous situations. Participants in the HAZOP review are usually the members of the technology transfer teams.

The production plant will eventually produce three validation lots of drug substance, using the chemical process intended to manufacture commercial supplies, in production sized equipment. The actual scale of these lots may vary from a full (maximum) production run to a fraction thereof (usually one-half or one-third). These lots are used for the preparation of full scale drug product batches, for the drug product primary stability studies.

B. Process Validation

Validation of drug product manufacturing methods and analytical assays have been FDA requirements for some time. More recently, the FDA has extended this requirement to the drug substance. There are some fundamental differences between the production of drug substances and drug products. The former is a chemical process resulting in chemical transformations and the creation of new compounds; the latter is a physical process, resulting from a physical mixing and physical interactions of the drug substance with a number of biologically inactive excipients. The exact application of all validation protocols from one to the other may not be suitable.

Both the FDA and the pharmaceutical industry have attempted to define validation in terms of the drug substance. It is generally accepted that *chemical process validation* consists of a number of components such as the following:

1. A reaction protocol is set up for each step of the chemical manufacturing process for the drug substance. This protocol is based on all the previous laboratory and pilot plant work and, in some cases, production experience. Three (3) consecutive production-size lots are produced following these protocols. Results should show that all previously defined specifications for intermediates and final product are met. There should be minimal or no deviation from the protocols.

2. A process validation document is generated. This is based on studies carried out during the normal optimization process or retrospectively to define critical and controlled operating parameters for each step of the process, with emphasis on the later steps of the synthetic sequence. Critical operating parameters are defined as variables within a process step that directly affect the quality of the material produced in that step. Controlled operating parameters are variables that are monitored during the manufacturing process and maintained within previously established limits. In many cases, the controlled operating parameters are justified by economic, operational, or safety considerations.

It is the responsibility of development chemists, working with personnel from production plants, to establish a process validation document, at about the same time as the relevant NDA is filed.

This document is generally not filed with the NDA, but should be available at the plant during a preapproval inspection. Preapproval inspections may occur as early as 3 months after NDA submission.

C. Regulatory

The chemistry, manufacturing and controls (CM&C) section of an NDA contains information on the synthesis of the drug substance. Details are often included in a Drug Master File (DMF) prepared by the manufacturer (not necessarily the sponsor of the NDA).

There are two types of relevant DMFs: DMF type I describing manufacturing site procedures, equipment, personnel, and organization and DMF type II describing a specific manufacturing product. The information contained in the type II DMF includes the following:

Description of the drug substance
Manufacturing directions for the drug substance
Materials controls
Drug substance controls
Specifications and test methods
Stability
Packaging and labeling

The DMF serves as a reference for both the FDA reviewing chemist and the field office conducting the preapproval inspection of the plant. This inspection is carried out to ensure that the manufacturer follows all steps and tests described in the DMF. The process validation document is also referred to and reviewed during this inspection. Clearly the purpose of such a document is to present evidence and data showing that both the development and production units have studied the process of manufacture in detail, and understand the scope and limitations of the reaction parameters used. The responsibility for a preapproval inspection lies primarily with the site organization. The R&D organization (Chemical Development, Analytical R&D and QA) generally provides assistance.

IV. RADIOCHEMISTRY

Another aspect of development of a new NCE is the synthesis of radiolabeled sample. The synthesis of these labeled compounds is the duty of a group of specialized radiochemists. Labeled compounds are used by drug metabolism for the study of the absorption, distribution metabolism, and excretion (ADME) of NCEs in both animals and humans. Most common radioactive labels used are carbon-14 and tritium (hydrogen-3). The approach to the synthesis of these compounds is dependent entirely on the availability of commercial "raw materials," namely compounds containing carbon-14 or tritium (e.g., $^{14}CO_2$, $Na^{14}CN$, T_2, $LiAT_4$, and other small molecules). The success of the synthesis depends on the efficient use of these expensive small molecules. The syntheses are generally carried out on mg scale using other reagents or reactants in excess, and may use purification methods (e.g., column chromatography) that would be impractical for the preparation of nonradioactive materials. A radiochemical group, in addition to being regulated by the FDA, Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA), is also responsible to and licensed by the Nuclear Regulatory Commission (NRC) for

TABLE 1 Summary of the Major Chemical, Manufacturing and Controls (CM&C) Activities

	Chemical development	Analytical development	Pharmaceutical development
Preclinical	Preparation of drug substance by original medicinal chemistry route. Evaluation of this synthesis for scale-up.	Development of preliminary assay.	Preformulation. Development of initial formulation.
Phase I	Initial process development. Preparation of drug substance, 1–5 kg scale.	Definition of IND analytical methods. Preliminary degradation studies.	Formulation development for clinical studies. Clinical supply preparation.
Phase II	Additional process development; choice of final manufacturing method. Preparation of developmental supplies, 10–50 kg.	Analyses of samples from chemical development. Development of analytical methods for the drug product.	Final formulation development. Clinical supply preparation. Preparation of biobatch.
Phase III	(In cooperation with personnel from manufacturing site) Optimization of manufacturing method; scale-up. Preparation of clinical and validation lots. Validation reports.	Final analytical method. Degradation studies. Identification of all impurities. Primary drug substance and drug product stability sample analyses.	Scale-ups. Validation batches. Drug product primary stability studies.

control of radioactivity. The disposal of radioactive wastes has become a major consideration for a radiochemical laboratory. In the past, these wastes were absorbed onto inert absorbents, packaged in double-walled containers, and disposed of by companies specializing in waste disposal. Many states have now closed disposal sites. Wastes currently generated need to be stored indefinitely on site, creating a safety hazard. Minimization of these wastes, therefore, becomes a major part of the synthetic strategy.

V. SUMMARY

The major chemical, manufacturing, and controls (CM&C) activities are summarized in Table 1. Decisions on the timing of individual activities within a department and the coordination of these activities between departments is crucial to the efficient use of resources and to the submission of a timely and quality NDA.

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6

Formulation Design Considerations

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I. INTRODUCTION

The decision to proceed to clinical evaluation of a new chemical entity is a major commitment of resources in an ever increasingly competitive environment. This decision initiates a cascade of events to support that first dosage to humans: drug metabolism and pharmacokinetic studies, toxicological evaluation, synthesis of drug substance, initiation of formulation development, and evaluation of analytical methods. Often these issues are so tightly interconnected that a change in one strategy affects the others. For example, a modification in drug substance crystal structure effected by an altered recrystallization route could affect dissolution rate with consequences on oral bioavailability, systemic exposure in toxicology studies and the processability or stability of the drug substance in formulation work. If such an event were to happen in the midst of product development, it could have a large negative impact on the time lines of clinical evaluation. It is in the best interest of the company and the public to get novel therapeutic agents to the market as rapidly as possible. Pharmaceutical product development plays a central role in this process by making dosages available for evaluation in clinical trials. In most pharmaceutical companies, the scope pharmaceutical product development spans from the handover of the molecule from the discovery scientists to the transfer to commercial manufacturing sites. This is clearly too large a scope of activity to cover in this forum. Therefore, this chapter focuses on the activities that can ensure a rapid, reliable process to initiate clinical evaluation.

II. PHARMACEUTICAL DEVELOPMENT ASPECTS OF DRUG SUBSTANCE

A. Selection of Salt and Crystal Form of New Chemical Entity

If the molecule of interest is ionizable, selection of the counterion with which to proceed has to be considered. The pKa of the parent molecule must be known before initiation of salt selection (see later), and generally the selection is determined empirically from a shortened list of potential, pharmaceutically acceptable counterions. Among the considerations in selecting a final salt form for subsequent development are ease of formation and yield, chemical and physical stability of the final form, the salt's aqueous solubility, and characteristics for ease of subsequent manufacture. References 1 and 2 are comprehensive reviews of the salt selection process.

Many substances can occur in forms having differing crystal habit or solvated forms. During the salt selection process, attempts generally are made to minimize the potential for multiple forms of the drug. These differing forms of the same molecule can affect dissolution rate and hence bioavailability, stability, and manufacturability, all of which can have an impact on formulation

development. Because of these factors, consideration for the proper crystal modification to be developed for clinical evaluation should occur early in development (3,4). The selection of an appropriate salt form and crystalline form with which to proceed in development is accomplished most effectively by collaboration among discovery, chemical process development, and formulation development scientists. The discovery chemist is the most knowledgeable about the molecule in early development and would have the most insight on behavior of the molecule observed during the discovery phase. Information on such topics as variable crystal habit upon recrystallization, hygroscopicity, particle size variability, and solubility, for example, would give development scientists insight as to approaches to explore in getting to an appropriate drug substance for development. Time spent early in this phase of development selecting the appropriate form of the new chemical entity to move forward minimizes the eventuality of unexpected product-related findings later that could have an impact on clinical progression. Changes in salt and polymorph form may require additional preclinical and clinical safety studies (5). The susceptibility of a molecule to have multiple crystal habits or solvates is dependent on the structure of the molecule and is not easily intuitively predictable. A noncomprehensive list of molecules with known polymorphs or solvate modifications is given in Table 1.

A knowledge of how polymorphs are formed for a given molecule is critical for a number of reasons: (a) to ensure that the drug substance is consistently the desired form, (b) to protect the drug product from conditions during manufacture and storage that are known to elicit crystal changes, and (c) to exclude others from finding an alternative crystal form with more desirable pharmaceutical product characteristics. The examples in Table 1 demonstrate the importance of investigating crystal habit early in development. Crystal form can

TABLE 1 Incidence of Varying Crystal Habits in Drugs and Detection Techniques

Drug	# Forms	Techniques	Reference
Fosinopril	2	DSC, TGA, powder x-ray, FTIR, solid state NMR	6
Carbovir	5	DSC, TGA, powder x-ray, FTIR, thermal microscopy, SEM, dissolution studies	7
Moricizine	2	DSC, FTIR, powder x-ray	8
Diflunisal	4	DSC, FTIR, thermal microscopy, dissolution studies	9
Rifamexil	5	DSC, FTIR, powder x-ray, TG, thermal microscopy	10
Phenobarbital	5	DSC, powder x-ray	11
Losartan	2	DSC, powder x-ray, TGA	12

change upon storage after dosage form manufacture. Anhydrous theophylline prepared in a tablet dosage form and stored in high humidity coverts to theophylline hydrate, which appeared on the surface of the tablet. Not unexpectedly, this change in the hydrate of the drug substance had significant effects on the performance of the dosage form (13, 14). Processes involved in manufacturing, such as grinding, compression, or mixing, can also effect a change in crystal form. For example, grinding of cortisone acetate has been shown to cause polymorph I to convert to form II (15). To avoid these problems, screening for crystal modifications should be complete before initiation of preclinical safety assessment studies that will support clinical development. This evaluation can be effected in a number of ways: for example, altering recrystallization solvents and temperatures, changing the concentration of the drug in the recrystallization solvent, exposing purified drug substance to varying humidity conditions, and performing compaction stressing of the drug substance.

Table 1 also lists the multiple analytical techniques available to evaluate crystal modifications. The listed techniques allow comparative interpretation of putative modified crystal forms, detecting changes in crystal form or solvate. To obtain absolute information on crystal habit, single crystal diffraction x-ray crystallography must be used. This technique is generally limited to use with drug substance and cannot be used with formulated material.

B. Preformulation Studies

Before initiation of product development activities, a general knowledge of the physicochemical properties of the molecule should be obtained to ensure that potential formulation strategies are consistent with the chemistry of the molecule. For these studies, the availability of a stability-indicating analytical method is an absolute necessity. However, at this point in the development cycle, such a method often has only begun to be evaluated. A differentiating method will evolve as preformulation studies progress. It is good practice to ensure that the method used to monitor the initial studies has been at least demonstrated to be linear, accurate, and precise and to have the capacity to resolve solution degradation products generated by artificial stress conditions, such as heat, pH extremes, and light. These artificial condition samples should not be so stressed as to have little or no active present, since the degradation products may not be representative of what will likely be encountered in the preformulation studies or in a prototype formulation stability study. Rather, the conditions should be tailored such that loss of active is in the 5% to 10% range with a near concomitant increase in degradation products. As preformulation studies progress, the method will likely need to be adjusted to resolve new degradation products or excipient-related components. Reference 5 gives some guidance as to the expectation of an analytical method for early development.

Because the aqueous solubility of a molecule can be used to assess so many different pharmaceutical parameters, ranging from interpretation of preclinical oral availability studies to prediction of chemical stability during manufacture and storage, it is generally the first study to be performed on the molecule. If the molecule is not ionizable, the solubility is usually determined near physiologic pH. If the molecule is ionizable, the solubility studies should be conducted over a pH range that minimally parallels that encountered in the gastrointestinal tract, pH 1.2 to pH 7.0, using appropriate buffers. It is important to ensure that these experiments are conducted at a given, controlled temperature and that the pH is recorded after the drug has come to equilibrium with the solvent. Additionally, buffer concentrations should be kept minimal so as not to interfere with the measurements. Often in early development, the availability of the drug substance is quite limited. If the molecule is freely soluble in water, considerable drug substance can be used unnecessarily for these early studies. In such cases, a predetermined upper limit of solubility can be set and minimal volumes of solvent used to conduct the study. Note that these samples can also be used as the pH stress samples to confirm the specificity of the analytical method. The output of a pH-solubility experiment is a plot of aqueous solubility versus pH. An estimate of the pKa of simple ionizable molecules can be obtained with these data. For example, solubility data on a series of analgesics has been used to calculate their pKa's (16).

Knowledge of a molecule's pKa is basic to understanding both physicochemical and bioavailability data. Reference 17 is a good review of techniques available for such determinations. For molecules with sufficient aqueous solubility and sufficient resolution between multiple pKa's, aqueous titrations generally yield accurate data. Numerous techniques have been applied to obtain pKa's in various matrices: 1H-NMR has been used to determine the pKa of chlorpromazine in lecithin vesicles (18); isotachophoresis has been used to compare pKa's of simple bases to conventionally derived values (19); a spectrophotometric method has been used to measure the pKa's of several thiazides (20). The pKa of molecules having limited aqueous solubility can be determined using nonaqueous titrimetry (21) or by potentiometric titrations in methanol-water systems (22).

An important factor governing the absorption of a drug following oral administration is its lipophilicity. For new chemical entities, the partition coefficient of the neutral species, P, is an appropriate measure of lipophilicity. For a compound that is ionized at physiological pH, the distribution coefficient, D, is a better measure of its ability to cross lipophilic membranes. The time course of drug activity, drug blood levels, and levels in other body fluids will depend on a number of factors including solubility and metabolism, but the partitioning properties of the drug are also important as they are likely to have

some influence on its permeation rate through membranes and on its accumulation in fatty tissue. The observed activity of a drug is a function of its intrinsic activity and concentration at the active site. There are number of examples (23, 24) of relationships between intrinsic activity and partition coefficient (P), and this is to be expected when hydrophobic interactions are important for drug binding. Futhermore, partition coefficients are widely used in evaluating structure and activity relationship of new chemical entities. Important applications of partition coefficient in pharmaceutical development include selecting appropriate additives such as emulsifiers and oils in preparing formulations. An understanding of the partitioning properties of a new chemical entity is also critical in designing efficient extraction procedures and selecting appropriate contact tubing materials, which the new chemical entity may encounter during processing. Several methods to determine partition coefficients are well described in reference 25.

The pH-stability profile of a molecule should be determined if there is reason to believe, based on structural features, that the molecule may be susceptible to pH-dependent degradation. While such studies are of paramount importance when formulating aqueous solutions, for oral solid and semisolid dosage forms they are of less importance unless the molecule exhibits unexpected degradation in the dosage form or if the molecule can undergo degradation in the gastrointestinal tract thereby having an impact on oral bioavailability (26, 27). pH-stability studies are set up to monitor a molecule's stability at multiple, fixed pHs over time at a given temperature and ionic strength. At each pH, the loss of active is monitored over time and is plotted as fraction of active remaining versus time. The slope of this line is the observed rate constant for degradation at this pH. These data are collected at multiple pHs, and the observed rate constants are plotted as a function of pH to generate a degradation rate versus pH profile (28). pH-rate studies are also used to evaluate the effect of formulation excipients on product stability. For example, pH-rate profiles, or limited versions thereof, have been used to demonstrate that cyclodextrins stabilize progesterone derivatives (29, 30), indomethacin (31), thymoxamine (32), and cyclopentolate (33); to demonstrate that glutathione stabilizes the photodegradation of dacarbaxine (34); and to characterize the stability of emulsion formulations of clarithromycin (35).

Metal ions present in trace levels in either the drug substance or excipients can have a deleterious effect on product stability. If the molecule under development is susceptable to metal-catalyzed degradation, studies should be conducted to investigate this potential. Generally, copper and iron cause these problems in pharmaceutical products. The stability of captopril in aqueous solutions has been studied and found to be sensitive to metal catalyzed oxida-

tion. Addition of a citrate buffer to chelate the metal ions significantly reduced this degradative pathway (36). Similarly, mitoxantrone has been stabilized by inclusion of both an antioxidant (sodium metabisulfite) and a metal chelator (EDTA) to the formulation (37).

To evaluate gross incompatibility with potential formulation excipients, studies should be conducted with potential excipients to screen out those that are incompatible. These data can be obtained under accelerated stability conditions using prototype formulations or can be conducted in binary or tertiary mixtures of drug substance with potential excipients. The former approach requires significant product development activity using a considerable amount of drug substance. The latter approach consumes much less drug substance and allows for more latitude in screening excipients (38). While conducting studies on simple mixtures does not substitute for full fledged stability studies on formulation prototypes and is not necessarily predictive of stability of the manufactured dosage form (39), useful information is often gathered and significant saving of time and drug substance can be effected by conducting such studies before the formulation of prototype studies. Additionally, these studies can identify early any potential excipient-excipient interactions that can complicate analyses (40). There are several sources of information on excipients that are in approved drug products (41–43). Additionally, The Code of Federal Regulations (CFR) Section 184 lists direct food substances that are generally recognized as safe (GRAS), and Section 172 lists food additives permitted in foods when used in the quantities and applications defined.

III. PRECLINICAL EVALUATION OF ORAL BIOAVAILABILITY LIMITATIONS

Generally, pharmaceutical firms prefer to develop an oral route of administration for a new chemical entity. Dosage forms associated with this route are relatively cheap to manufacture, are simpler for patients to handle, and are widely accepted by the public. Because this is the preferred route of administration, it becomes critical to evaluate the oral bioavailability of lead compounds in the earlier stage of the development process. Oral bioavailability of a compound can be a major selection criterion for the development candidate.

Understanding a compound in terms of its oral bioavailability could provide a significant insight as to how to develop the compound and dictate the strategy of the formulation development approach for a specific molecule. Drawbacks of the low bioavailable compound from a pharmaceutical development standpoint are inherent variability in the oral bioavailability, a requirement of large quantities of drug substance to establish a safety margin in preclinical safety studies, and, depending on the pharmacology of the molecule, a high

dose to elicit the desired affect. Clinically, this shortcoming of the molecule translates to the need for a large clinical trial population to demonstrate a wide therapeutic and safety margin.

Generally, poor bioavailability can be categorized into one or more of the following four categories: dissolution rate limited availability, degradation in the gastrointestinal tract (44, 45), poor membrane permeability, and rapid elimination. Reference 46 reviews the consequence of these factors in bioavailability. The discovery of new chemical entities can address the bioavailability issue by building a molecule optimized not only for biological effect but also for oral availability. These two factors may be mutually exclusive, and the result of the search may not yield an ideal candidate. Techniques are available for quickly assessing the permeability through systems representative of the human intestinal tract.

In vitro and in situ experimental models that are descriptive of in vivo drug absorption are valuable tools in the discovery of new chemical entities with the potential of oral bioavailability. The intestinal absorption models most widely used in this assessment are (a) the rat in situ single-pass intestinal perfusion system, (b) the rat everted intestinal ring method, (c) segmented intestinal tissue transport method using Ussing Chamber (47), and (d) monolayers of human colon adenocarcinoma cell line (CACO-2) (48).

A. Everted Rat Intestinal Rings

Everted rat intestinal rings offer a relatively quick and inexpensive technique for measuring uptake of drug into tissue. Rings can be prepared from virtually any segment of intestine, permitting study of axial differences in uptake. This technique has been widely used in mechanistic studies of amino acid and peptide transport and has a wide database in the literature (49). Critics of this method take issue with the variability of the tissue over the time course of the experiment, although ring incubations require a small fraction of the time used for everted intestinal sac or excised tissue experiments. The technique is limited to uptake of drug by the tissue, unlike excised tissue preparations where transmucosal flux can be monitored (50). One of the most important considerations is whether to use everted rings if the compound of interest is available in radiolabeled form; analysis of nonradiolabeled drug in intestinal tissue is relatively labor-intensive, although necessary when one is interested in obtaining metabolic information (51). This technique offers logistic advantages over some others. The everted ring technique does not entail the considerable time and expense of start-up and maintenance of the CACO-2 cells, nor does it require the greater number of animals, with associated husbandary costs, nor the need for statistical power of the perfusion method. There is a statistical advantage in that several conditions can be studied in replicate, with controls obtained from the same animal.

B. Rat Single-Pass Intestinal Perfusion

Rat single-pass intestinal perfusion is an in situ technique wherein the blood supply, innervation and clearance capabilities of the animal remain intact. Input of drug can be controlled in terms of concentration, pH, osmolality, composition, intestinal region, and flow rate (52). This absorption model is physiologically and pharmacologically responsive, which may account, in part, for the higher variability observed in some of these experiments. The drug is measured in buffer or perfusate, thus facilitating assay by drug-specific chromatographic means. This technique has been used extensively in establishing a database of permeabilities with correlation to human absorption data, as well as to elucidate absorption mechanism (53, 54).

C. Tissue Transport Using Ussing Chambers

In vitro tissue transport evaluations using Ussing chambers have been widely used for studying intestinal permeability since the 1960s. The Ussing technique provides a method for comparing intestinal epithelial permeability of molecules while also monitoring intestinal viability and integrity. Depending on the permeability of the compound, both uptake and transport can be determined. The use of radioisotopes is useful when no sensitive assay is available. Another major advantage of this system is comparison of segmental differences in transport. The tissue transport system using the Ussing technique does not provide information on the potential hepatic first-pass effects or instability in any compartment other than to the intestinal epithelial cells. It does afford a quite rapid screen with a rough correlation of permeability to human bioavailability (Fig. 1).

D. CACO-2 Cell Monolayers

CACO-2 cell monolayers have evolved to a widely used model for intestinal absorption with a burgeoning database in many laboratories. This system offers the convenience of a continuously cultured cell line to model the small intestinal epithelium in a cell line derived from human colon adenocarcinoma. The preparation of a fully differentiated confluent cell monolayer requires about 3 weeks. Recently, Biocoat Intestinal Epithelium Differentiation Environment (BIEDE), a ready-to-use confluent and fully differentiated CACO-2 cell monolayer in 3 days, offers a more convenient and productive absorption screening tool (55). The human origin of cells is desirable; however, the transformed nature of the cells may result in unpredictable differentiation markers (53). In addition, several reports have associated transepithelial electrical resistance, enzyme expression, and some transport properties of the CACO-2 cells more closely with colon than small intestine (54). Transport can be measured by

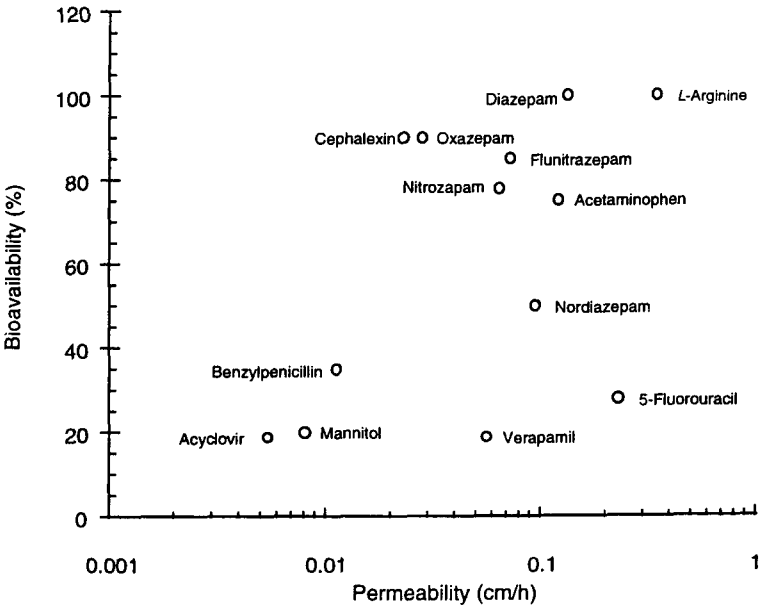

FIG. 1. Bioavailability in man versus in vitro rabbit ileal permeability. From PL Smith (47) with permission.

transcellular flux or uptake directly into the cell monolayers, thus isolating apical and basolateral membranes processes. Measurements of drug are made either in buffer or from lysed and precipitated cells, thus minimizing assay difficulty.

IV. PRECLINICAL EVALUATION OF FORMULATION STRATEGY: IN VIVO ANIMAL MODELS

The in vitro permeability studies described previously are designed to identify molecules with transport attributes, which look promising for a clinical lead. Salt and crystal form studies have identified the appropriate form of the molecule to proceed. The next step in the progression is to test the selected molecule in an appropriate animal model using simple oral routes with comparison to intravenous administration. The key issue animal studies can address is to predict the performance in human.

A. Animal Size

An important factor in determining the choice of animal species for bioavailability testing is its size. In most circumstances, it is not possible to ad-

minister intact, solid pharmaceutical formulations, tablets and capsules for example, in small rodents such as mice, rats, or hamsters. If such dosage forms are to be tested, larger species, such as rabbits, dogs and monkeys, must be used.

Another problem associated with the use of smaller species is repetitive blood sampling. Urine measurements of drug excretion can be used for all animal species to determine bioavailability, overcoming many of the blood sampling difficulties. A reasonable proportion of the drug, however, must be excreted unchanged via kidney to make the results meaningful. In addition, extensive first-pass metabolism would preclude this approach if the total metabolite excretion is being used.

B. Gastrointestinal pH

A hypothesis that has found widespread acceptance among scientists studying drug absorption is the pH partitioning hypothesis, which contends that primarily the lipid soluble, non-ionized fraction of the drug in solution crosses the intestinal wall. Consequently, it would be expected that the pH of the gastrointestinal tract, and hence the degree of ionization of the drug molecule, would have a profound effect on drug absorption. The gastrointestinal pH, therefore, should be an important determinant in the selection of animal species (Table 2). Compounds such as cimetidine (56) are significantly affected by gastric pH in terms of the plasma concentration-time profiles. Additionally, ionized molecules have shown significant absorption, albeit at a slower rate (57).

C. Gastrointestinal Motility

All animal species suffer from the disadvantage of shorter gastrointestinal transit time compared to humans, ranging from 6 to 8 hours in rat (60) and from 14 to 18 hours in dog (61). This could have profound consequences on the

TABLE 2 Gastric and Intestinal pHs for Different Animal Species[58,59]

Gastrointestinal section	pH Values					
	Rat	Guinea pig	Rabbit	Dog	Monkey	Humans
Stomach	3.3–5.5	4.1–4.5	1.9	3.4–5.5	2.8–4.8	1.5–3.5
Duodenum	6.5–6.7	7.6–7.7	6.0–6.8	6.2	5.8	5.0–7.0
Jejunum	6.7–6.8	7.7–8.1	6.8–7.5	6.2–6.6	5.8–6.0	6.0–7.0
Ileum	6.8–7.1	8.1	7.5–8.0	6.6–7.5	6.0	7.0
Colon	6.6	6.7	7.2	6.5	5.1	5.5–7.0

bioavailability of drugs that are only absorbed from a narrow section of the intestinal tract, since the amount absorbed depends on the residence time of the drug at that site. For example, ranitidine (62) and pafenolol (63) exhibit region-specific availability in the intestinal tract.

D. Strategy

Because of the variability of in vivo bioavailability testing, formulation evaluation using animal models will continue to present a challenge to correlate to humans. When undertaking any preclinical bioavailability study, considerable thought must be given to the experimental design, with well-defined objectives and a full realization of the possible limitations. Probably one of the most important and difficult aspects of the experimental design is the choice of animal species. Before embarking on any in vivo-bioavailability testing using animals, investigators should ask the following questions (58):

1. What information is needed?
2. Can we use humans?
2. If not humans, what species is most appropriate?
3. Are the kinetics in that species linear at the dose level to be used?
4. Can data from that specie be modeled to humans?

None of animal models are ideal, and each has its advantages and disadvantages (Table 3). Nevertheless, many investigators have used animals for bioavailability testing and have obtained valuable information that has helped in their understanding of their product (Table 4). Of the species listed in Table 3, rabbit appears to be the least suitable animal model for bioavailability test-

TABLE 3 Advantages (+) and Disadvantages (-) of Different Animal Species as a Model for Human's in Bioavailability Testing (58)

	Rat	Rabbit	Dog	Monkey
Cost	+	+	-	-
Ease of urine collection	+	+	+	-
Ease of blood sampling	-	+	+	+
Ease of handling	+	+	+	-
Intact solid formulation	-	+	+	+
Intestinal pH	+	-	+	+
Gastrointestinal transit time	-	-	-	-
Gastrointestinal microflora	-	-	+	+
Drug metabolism	-	(-+)	(-+)	+
Biliary excretion	-	+	-	+

TABLE 4 Examples of Uses of In Vivo Animal Models for Bioavailability Testing

Species	Drug	Testing	Reference
Dog	Danazol	Nanoparticle	64
Dog	Cinnarizine	Cyclodextrin complexation	65
Dog	Dicumarol	Effect of particle size	66
Dog	Dicumarol	Effect of particle size and crystalline form	67
Dog	Sulfadimethoxine	Bioavailability from oral suspension	68
Rabbit	Griseofulvin	Dissolution versus bioavailability	69
Rat	Amiodarone	Effect of surfactant	70
Rat	Griseofulvin	Effects of lipids	71
Rat	Sulfisoxazole acetyl	Effects of lipids	71
Rat	Sulfafurazol	Effect of additives	72
Rat	Penicillin and cephalosphorins	Bioavailability	73

ing, despite its relatively large size (large enough to test solid formulations) and low cost. This is because it has a long gastric emptying time, and both its gastrointestinal pH and microflora bear little resemblance to those in humans. Rat has the major disadvantage of being too small to test most solid formulations, as well as being difficult to obtain multiple blood samples from repetitive sampling. In addition, the gastrointestinal microflora is different from that of humans. This species does have the advantage of having a gastrointestinal pH similar to that in humans and, if urinary data are used for bioavailability testing, it is easy to obtain total urine collections using all-glass metabolism cages.

In most respects, the monkey offers the closest physiological and metabolic model for humans and would be the first choice if not for its extremely high cost and handling requirements. Additionally, the monkey is capable of transmitting several human pathogens, and care must be taken when handling analytical samples. Obviously, if primate facilities are routinely available, the use of this species becomes more attractive.

Dogs offer a reasonable compromise since (a) they are large enough to test solid dosage forms, (b) their gastrointestinal pH is similar to that in humans, (c) sampling is convenient, (d) they are easy to handle, and (e) special precautions are not needed when handling the biological samples after collection. There are occasions, however, when metabolic and enterohepatic circulation considerations preclude their use as a test species for bioavailability testing. If

this should occur, the choice usually becomes limited to monkey, if applicable, or humans.

The result of the preclinical bioavailability assessment will be a knowledge of the factors that the formulation development scientist must consider in designing a formulation.

V. FORMULATION STRATEGIES

A. Nonlimiting Oral Bioavailability

The formulation strategy taken for initiation of early clinical development depends on several factors and always assumes the critical nature of initiating such studies in an expeditious fashion. If preclinical studies indicate that the molecule has acceptable oral bioavailability based on its pharmacological end-point, then the most straightforward approach is to dose orally using a simple dosage form. Examples of such simple oral dosage forms are as follows:

1. Solutions
2. Encapsulated drug substance
3. Encapsulated nonaqueous suspensions
4. Encapsulated formulated drug substance

Each of these approaches has its own merits and limitations depending on the characteristics of the drug substance, the availability of the drug substance, the doses to be administered, and the design of the clinical protocol.

Oral solutions afford great flexibility in dosing over large dose ranges that may be needed in an early clinical trial, and dosing can be easily tailored specifically to the patient. Additionally, such an approach minimizes the amount of drug substance required to support both the clinical evaluation and stability studies monitoring the time from manufacture to dosing. In the simplest approach using this strategy, the clinical pharmacy prepares the dosing solution as needed. Therefore, by and large, stability studies on the drug substance support the trial. The stability of the dosing solution has to be demonstrated over the time course of solution preparation to dosing. Alternatively, a clinical trial manufacturing facility would manufacture a bulk solution for shipment to clinical trial sites where the solution would be dosed as needed. In this latter scenario, stability studies on the bulk drug solution would be required. While this approach at first looks to be a facile route to rapid clinical evaluation, other factors can come into play that could limit its utility. First, the drug must be soluble in the dosing solution to the extent that all doses can be attained in a reasonable dosing volume, and if the dosing volume has to be changed to attain higher doses, the change in volume should have no effect on bioavailability. Another consideration is that trial blinding, if needed, may not be possible due

to taste, coloration, odor, etc. If multiple centers are to be used in the clinical evaluation, a further consideration in taking this approach is that control of the manufacture is not centralized. Quality issues must be carefully scrutinized on a case by case basis to ensure dosing consistency, safety, and trial integrity. Finally, since this approach would not likely be applied to trials with a large number of subjects, plans for bioequivalence to the subsequent formulation(s) have to be built into the plan in anticipation of moving to larger scale trials where dose ranging would occur.

Encapsulated nonformulated drug substance also affords significant flexibility in dosing over large dose ranges, allows for patient specific dosing, and minimizes the amount of drug substance required to support the clinical evaluation. As was the case in the example of the oral solution, bulk drug stability studies would provide the main data in support of the trial, supplemented by that required by the time the drug substance was stored in the capsule. If these early trials were sufficiently small, as was the case for oral solutions, the dosages could be prepared in the clinical pharmacy and immediately dosed. Therefore, the duration of the stability study on the "formulated product" would be quite short when compared to conventional formulations. This approach affords great flexibility in sourcing clinical protocols as long as the drug substance can be accurately and reproducibly weighed in the clinical pharmacy setting. This approach eliminates some of the limitations of the oral solution approach; that is, blinding is possible and dosing volume is not a concern. However, as stated earlier, the potential exists to lose control over the manufacture of the dosage if adequate quality control is not ensured in the clinical pharmacy. If this approach were used in clinical safety studies, bioequivalence to dosage forms subsequently used in clinical evaluation would have to be anticipated.

Oral solutions or drug substance in a hand-filled capsule prepared in a noncentralized clinical trial supply manufacturing setting offer advantages of speed to clinical evaluation and conservation of a limited supply of drug substance. However, support systems must be in place to ensure that all documentation required for the preparation and monitoring of such manufactures is available and that strict adherence to cyclic guanosine monophosphate (cGMPs) are supported by those systems. Utilization of these approaches must ensure adequate monitoring of the preparation of the dosages to ensure quality of the product and appropriate interpretation of the results.

Another approach that allows for a relatively rapid route to clinical evaluation is encapsulated nonaqueous solutions or suspensions of a drug substance. This approach can be considered from the perspective of a dosage form manufactured both at the site of the clinical trial and at a centralized clinical manufacturing facility. Both approaches allow for broad dose ranges, depending on either the solubility of the drug substance in the nonaqueous matrix or the ability of the formulation to support the suspended substance. For a suspension for-

mulation approach to be viable, validation must ensure that the drug substance is uniformly suspended in the nonaqueous matrix. The formulation can be filled either into hard gelatin capsules and sealed (74, 75) or into soft gelatin capsules at a contract manufacturer. As in the preceding cases, this approach also has the potential for preparation of dosages at the clinical site, thus minimizing the drug substance requirements to support premanufactured dosage units. Drug product stability data can be gathered in the bulk form, with sufficient data generated to support the time the formulated material is in the capsule before dosing. Blinding is easily attainable. This approach has a potential advantage over the aqueous solution and encapsulated drug substance approaches in that this dosage form can be commercialized.

The final relatively simple manufacturing approach that can be used for clinical evaluation is formulated drug substance in powder-filled capsules. While this approach requires sufficient preformulation work to ensure that the drug is stable in the formulation, it does not require the extent of formulation development required for tablet development. This approach does not have the potential for as large a dose range as the other approaches described. However, it does offer some flexibility in adjusting fill weights to attain multiple dosage strengths with a common blend. Generally, dosage units are not filled in a clinical setting using this approach, as confirmation of dosing would be difficult due to the potential of blend inhomogeneity. Manufacturing occurs at a clinical trial supply manufacturing facility, and full stability studies on manufactured dosage units would be required to support this approach. Therefore, while this approach conserves the drug substance that would be used in a tablet development program, it consumes considerably more drug substance than the other approaches described.

B. Tablet Formulation Via Direct Compression or Via Wet Granulation

It is conceivable that this approach will require substantial amount of drug substance and up-front resources to evaluate the new chemical entity for phase I. This approach is usually applied in the event the drug substance amount is not limited and the tablet dosage form is absolutely essential for the final dosage form. Tablet dosage forms can be achieved via direct compression process or via wet granulation process. Wet granulation development will require even further substantial resources for the development and optimization of the processing parameters. The drug substance requirements are very dependent on the scale of equipments available for the various processing steps such as granulator, mixer, dryer, and coating pan, if applicable. Often internal granules are made by a wet granulation process, and the common granules are further diluted by different ratio of external excipients so that a variety of strengths can be provided for phase I. However, care should be taken that the ratio of the

internal granules is relatively low; otherwise inhomogeneity of the dosage form for the low strength tablets can become an issue. Direct compression is generally the choice for the phase I tablet dosage form because it is simpler and requires a relatively short time for development. When the dose strength is relatively high, the tablet size will be dependent on the compressability of the drug substance. Tablet dosage forms are a viable approach if the drug substance amount is sufficient and dosage form development is not on the critical path to the progression to phase I. Tablet presentations in early development will yield information that will be more relevant to subsequent development than the other approaches described. Any problems associated with tablet formulations will be discovered early in development. However, thorough preformulation studies should minimize any unexpected findings.

C. New Chemical Entities Having Limited Oral Bioavailability

The preceding scenarios depict simple formulations designed to minimize resources for initiation of clinical evaluation of a new chemical entity. These approaches are viable if the molecule has sufficient oral bioavailability to support the intent of the first trials—safety and assessment of a relevant pharmacological end-points, if possible. If preclinical studies indicate that the molecule lacks sufficient oral availability to assess the intent of the first trials, however, more sophisticated approaches have to be considered to ensure exposure. The cause of poor bioavailability has to be assessed before rationally designing a formulation. Generally, poor bioavailability can be categorized into one or more of the following four categories: dissolution rate limited availability, degradation in the gastrointestinal tract (76–78), poor membrane permeability, and rapid elimination (79). There are formulation strategies that can address all but the last of these scenarios to varying degrees of success, depending on the molecule.

1. Dissolution Rate Limited Bioavailability

Dissolution rate limited bioavailability can be addressed in several ways: (a) reducing the particle size of drug substance to increase the surface area and, therefore, the dissolution rate, (b) altering the form of the drug to one that has enhanced solubility, and (c) including a solubility enhancer in the formulation. Particle size reduction has been used to increase the absolute oral bioavailability of danazol in dogs from 5.1% (mean particle size of 10 μm) to 82.3% for an aqueous dispersion of nanoparticules (mean particle size of 169 nm) (64). The absolute oral bioavailability of panadiplon, a sparingly soluble anxiolytic, has been evaluated in dogs after milling to specific particle sizes. The bioavailability of tablets manufactured using 100 μm drug substance is 24% and that obtained from 8.8 μm drug substance is 81% (80). Modification of the crystalline state of medroxyprogesterone acetate to a stable partially amorphous form yielded

a human relative bioavailability 3.49 greater than dosage forms containing the conventional crystalline drug substance (81). Cyclodextrins have been used extensively to increase the solubility of poorly water-soluble drugs with varying success in increasing oral bioavailability. In the danazol example, a cyclodextrin-solubilized oral liquid formulation increased absolute bioavailability to 106.7%, which is statistically equivalent to the nanoparticle presentation (64). Spironolactone formulated as a cyclodextrin complex, dosed as a solid, yielded a relative bioavailability 2.5 times that of the commercial spironolactone tablet (82). Assessment of cinnarizine orally administered to fasted dogs in a suspension, a capsule-containing drug substance, a cyclodextrin solution, or as a cyclodextrin inclusion complex in a capsule yielded absolute bioavailabilities of 8%, 0.8%, 55% and 38%, respectively (83).

In all these cases, reducing drug substance particle size, changing the crystalline form of the drug substance, and effecting enhanced solubility by addition of a derivatized cyclodextrin, the resulting increased bioavailability has been attributed to enhancing the solubility of the drug. However, increasing solubility or dissolution rate will not necessarily improve oral availability. The oral availability of a prodrug of the antiretroviral agent 9-(2-phosphonylmethoxyethyl)adenine is not affected by formulation in a cyclodextrin complex, a polyethylene glycol cosolvent system, or in aqueous suspension. In this instance, other factors influence bioavailability (84). All of these approaches are compatible with a first administration to humans as long as novel excipients used to prepare the dosage form, for example derivatized cyclodextrins, are supported by preclinical safety studies.

2. *Use of Permeation Enhancers to Increase Bioavailability*

Another approach applied to increase oral bioavailability is the use of permeation-enhancing agents. These agents function by altering, by varying degrees, the structural barriers present in intestinal tissue: mucus, intestinal cell membranes, the tight junction, the basement membrane, and the wall of the capillary. Permeation enhancers are often quite complex mixtures and include a variety of structural features, such as, but not limited to, ionic and nonionic surfactants, bile salts, fatty acids and derivatives, glycerides, and mixed micelles. Reference 85 gives an overview of the effects of numerous absorption enhancers. Bioavailability of the HIV-1 protease inhibitor, KNI-272, in rats has been enhanced by introduodenal administration of the drug in polyoxyethylated derivatized castor oil. The ID absolute availability of the molecule in 100% propylene glycol, a solubility enhancer, is 34.9%, whereas the enhanced formulation yielded 44.5% by the same route (86). A sodium oleate formulation has been tested in rabbits as a permeation enhancer for sulpiride. Based on area under the curve measurements, the enteric-coated oleate formulation is 2.6 times more available than the oleate-free formulation (87). A study of the effect of

TABLE 5 Comparison of Introduodenal to Oral Dosing on Bioavailability on Formulations Containing Permeation Enhancers

Compound	Dosage	ID/PO Availability
KNI-272	ID solution/PO solution	1.8
Sulpiride	Enteric capsule/uncoated capsule	3.3
Cefmetazole	Enteric capsule/uncoated capsule	3.1

chemical composition of medium-chain glycerides on the oral availability of cefmetazole in enteric-coated capsules has been studied in dogs. These data suggest that composition of the glyceride has an effect on availability with mixtures having higher glycerylmonocaprylate levels yielding higher availability (88). These examples, as well as others, also indicate that, as one would expect based on their proposed mode of action, the permeation enhancer and the drug have to be released in the same region at the same time to be effective. Additionally, the release has to be targeted to the small intestine (Table 5).

When designing a permeation-enhancing formulation for clinical evaluation, consideration must be given to the requirement of having both excipient and drug proximal. Usually, these liquid or semisolid formulations require liquid-filled hard gelatin or soft gelatin capsules as the dosage unit, putting an upper limit on the volume of permeation enhancer that can be used in a single dosage unit, approximately 0.6 to 0.7 ml. Additionally, to bypass gastric conditions that would in effect destroy the proximal requirement and negate any enhancement, the dosage unit has to be protected, usually by enteric coating. Technologies exist to perform enteric coating of both hard gelatin and soft gelatin capsules and is in routine use (89–91).

VI. SUMMARY

The pharmaceutical scientist has multiple formulation strategies to use in early clinical development. The approach selected depends on many factors, including but not limited to the following: physicochemical characteristics of the new chemical entity, the availability of drug substance, the presumed oral availability based on in vitro permeability studies or animal models, and the complexity of the formulation. While these approaches can initiate clinical trials, continuance of clinical development with a commercializable dosage form may require bioequivalence trials. The United States Food and Drug Administration (FDA) has stated that drugs with bioavailability problems will require demonstration of human bioequivalence whenever a change in formulation or manufacturing site occurs (92). A biopharmaceutical drug classification scheme (93) has been proposed for correlating in vitro drug dissolution to known human bio-

availability. The basis of the proposal is the recognition that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. The classification is as follows: case 1, high solubility-high permeability drugs; case 2, low solubility-high permeability drugs; case 3, high solubility-low permeability drugs; and case 4, low solubility-low permeability drugs. Based on this classification scheme, it is proposed that bioequivalence trials would be necessary for cases 3 and 4. It is suggested that for very rapidly dissolving, high solubility drugs (e.g., 85% dissolution in less than 15 minutes, with high permeability), a single point dissolution test is all that may be needed to ensure bioavailability (case 1). For slowly dissolving drugs having high permeability, a dissolution profile is required with multiple dissolving time points in systems that would include low pH, physiological pH, and surfactants, with the intent of demonstrating that the in vitro dissolution mimics the in vivo process (case 2). This classification scheme provides a basis for establishing in vitro-in vivo correlation that the formulation scientist must keep in mind from the initiation of product development.

Since the preferred route of administration for new chemical entities is oral, parenteral routes have not been discussed in this chapter. Formulations to support conventional parenteral routes (intravenous, subcutaneous, and intramuscular) are not generally problematic if the physicochemical characteristics of the molecule are such that it has sufficient aqueous solubility and stability to meet the requirements of the clinical program. For those molecules that do not fall into this category, solubility enhancers, stabilizers, and subsequent processing (lyophilization) have to be considered (94).

The goal of the early formulation development work is to provide a rationally designed dosage form for clinical evaluation. To meet this end, the formulation scientist must evaluate information on the physicochemical and biopharmaceutical characteristics of the molecule, thus ensuring that the formulation presents the best case for the molecule in clinical evaluation. Any early formulation proposal must be put in the context of the ultimate requirements of commercial dosage forms.

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Planning for Clinical Trial Supplies

Interaction Between Clinical Research, Clinical Manufacturing, and Clinical Packaging

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I. INTRODUCTION

One of the important facets in the drug development process is the provision of clinical supplies to be utilized in clinical trials. For each drug substance targeted for eventual Food and Drug Administration (FDA) approval, marketing, and distribution, a clinical plan is normally devised. This plan provides a listing of clinical trials required for approval, which will not only demonstrate safety and efficacy, but also desired timing. Delays in the clinical supplies process will not only upset this schedule but also the expected New Drug

Application (NDA) submission date. For a product that is predicted to earn $20,000,000/year, a delay of 1 day will translate in a dollar loss of approximately $55,000! It makes sense, therefore, to identify and address any or all issues associated with this process.

II. CLINICAL SUPPLIES COORDINATION

As described in the title of this chapter, the planning of clinical supplies is truly an art in dealing with the clinical research, clinical manufacturing, and clinical packaging groups. Coordination can be performed at project teams, by upper management, or via similar means. One of the current trends is to utilize pharmaceutics personnel as a clinical supplies liaison, medical coordinator, logistics coordinator, etc. The titles or names may be different, but the tasks that need to be performed are similar. The person or group of people that are the coordinators *should* have, although it is not mandatory, a background in at least one of the groups with whom they must deal. For example, an ex-formulator can always "learn" clinical packaging requirements and "understand" clinical research needs. Similarly, others will need to understand the requirements (i.e., [GMP]) in the manufacture and packaging of clinical trial supplies, as appropriate.

The coordinator can report to the Research & Development (R&D) pharmacy group, the medical group, project management, Regulatory Affairs, etc.; however, the tasks they need to perform are virtually the same. The coordinator needs to "coordinate" the actions of the three groups. Each of the three groups has priorities. In a corporation where the "pipeline" is full, there are several investigational drugs in various stages of clinical development. Where one clinical group is working on one cardiovascular drug, another on one asthma drug, another on one oncology drug, etc. all within one clinical research department, all of the clinical supplies requirements funnels to *one* clinical supplies manufacturing group and *one* clinical packaging group. This not only leads to setting of priorities but also how to handle *changing* priorities. Priorities can be set by the "first-come, first-serve" principle; however, problems may occur if one "gets in line" first but without all necessary documentation in place. Conversely, do high priority projects already take precedence? Does support for phase IV market products take precedence over investigational compounds, since the former is currently making money for the corporation while the latter *may* make money for the corporation someday? The liaison must realize that "seasonal" studies always have a high priority status along with those that need second or third packaging/manufacturing jobs. The liaison must have some authority to make these decisions. With this authority must come the credibility to make the "correct" decisions for the organization.

The liaison is also the focal point, obviously in communication between the three groups. The commitment has to be there to make sure that all details are finalized. Because of the crossing of department lines, the liaison must play an instrumental role in educating and/or training each of the groups in the other groups' capabilities and also their limitations.

The liaison must also be clearly visible as often as possible. This means visiting personnel from interested departments and not waiting for them to visit the liaison. Changes must be taken into account as soon as possible. Without these ongoing visits, study details may change while other departments continue with previous plans. What ensues may be chaotic.

The liaison must understand the manner in which medical personnel conduct their business. They need to deal with local clinical research associates, contract facilities of all types, outside investigators, Institutional Review Boards (IRBs), the FDA, and other worldwide regulatory agencies. If medical personnel do change their mind, it most likely is due to one or more of the aforementioned factors and not because they just want to alter the plans and upset the support personnel in the clinical supplies area. The liaison must be able to accept this fact and must also convey this information to affected groups. These groups must accept that they are support groups, along with the liaisons themselves.

In summary, the liaison must understand and be able to convey the clinical study process, confirm and reconfirm priorities, inform all groups as to progress, negotiate, educate and compromise. With all of this background, the liaison must be able to enact the process by several means.

III. BULK PRODUCT REQUEST

Any interaction between the three groups (i.e., medical, clinical manufacturing, and clinical packaging) must be confirmed via some sort of written system, authorizing the work to be performed. The written request system is the basis of all work. Areas that need to be specified are the amount of bulk quantity of different products to be manufactured, how studies are to be packaged, and obviously the timing of the work. The entire form for a bulk request for manufacture of supplies could contain the following information as noted in the accompanying sample form (Fig. 1).

Most areas are self-explanatory; the intention is to formalize the process of preparing bulk medication. Perhaps the most important areas to note are the "Date Requested" and obviously the products requested. The form theoretically is filled out and authorized by Medical Personnel however, the liaison has an integral part in the request as was noted.

Date Submitted: _____ Authorized by: _____

Date Requested: _____ Request No.: _____

Studies to be Used In: _____

Bulk Supplies

	Strength	Quantity	Lot #
Actives	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
Placebo	_____	_____	_____
Comparator Drug	_____	_____	_____
Comparator Placebo	_____	_____	_____

Assigned to: _____ (Manufacturing Manager)
Copies to: _____ (Manufacturing Director)
_____ (Analytical Director)
_____ (Clinical Packaging Director)
_____ (Quality Assurance Director)
_____ (Central File)
Date Available: _____
Approved by: _____ Date: _____

FIG. 1. Request for bulk medication.

The "Date Requested" must be staged sufficiently early to allow for the manufacture of the supplies followed by quality control release, quality assurance approval, and subsequent clinical packaging, labeling and distribution activities.

For example if a specific study needs to start on Day 0 then the actual manufacture of clinical supplies may have to begin on Day -60 to allow for all activities to be completed.

To save time, and if at all possible, it is beneficial to make sufficient bulk supplies for *several* studies. In this manner, only packaging and labeling activities may be required for the other studies, thus expediting their start data.

Large supplies of bulk may be prepared if certain criteria are met. The first concern would be availability of drug substance. Early in the Investigational New Drug (IND) process, typically small batch sizes of drug substance are prepared as synthetic techniques are optimized. Drug is not only needed for drug safety studies but for formulation development in planning future scale-up/optimization work in the pharmaceutics area. By obtaining a suitable quantity of drug substance for clinical supplies and manufacturing sufficient bulk prod-

uct, minimization of multiple GMP manufactures occurs along with saving time in the quality control (QC) and quality assurance (QA) departments. In addition, whereas only 10 to 20 capsules are needed for clinical supplies, many more capsules may be needed for QC testing, legal reserve samples, and stability testing. Minimizing the number of lots also minimizes the amount of drug substance required.

A second concern in the provision of bulk supplies is that the medical group can ensure their utilization for all planned studies. It does no one any good to make 1 million 25 mg capsules of Drug X if medical personnel use only 500,000 of them and then decide they need 40 mg capsules later in the clinical program. This is not only a waste of valuable time and resources, but also of precious quantities of drug substance.

It is also not wise to make the 1 million capsules if there is not sufficient stability data to support their use, either in bulk drums or in a specific container/closure system. There may not be considerable room temperature data but based on testing of samples stored at accelerated storage conditions, reasonable assurance needs to be given to allow for extended product use.

Very early on, before phase I, decisions need to be made regarding the dosage in these early studies. Clinical safety may be tested from 10 mg to 1,000 mg with various intermediate dosings. A possible scenario is presented in Table 1.

TABLE 1 Phase I Dosing for Drug X

Doses To Be Administered	Scenario #1
Placebo	4 × placebo
10 mg	1 × 10 mg
	3 × placebo
20 mg	2 × 10 mg
	2 × placebo
50 mg	1 × 50 mg
	3 × placebo
100 mg	2 × 50 mg
	2 × placebo
250 mg	1 × 250 mg
	3 × placebo
500 mg	2 × 250 mg
	2 × placebo
750 mg	3 × 250 mg
	1 × placebo
1000 mg	4 × 250 mg

Obviously, one could try to manufacture each of the nine products as individual entities; however, many of the higher strengths of drug may not fit into a reasonably sized capsule or tablet. A realistic scenario of dosing this sequence in a double-blind manner is noted in scenario #1. Only four products need to be manufactured (i.e., placebo, 10 mg, 50 mg, and 250 mg); however, each patient needs to take four capsules at one time. Another scenario could be to prepare only three products (i.e., placebo, 10 mg, and 50 mg), but this would entail patients taking 20 capsules in each dose group to "double-blind" the study. Compliance would be nightmarish; this scenario would never be acceptable.

The first scenario (i.e., four products) would most likely be accepted; planning for the higher doses needs to be included even though safety considerations during the conduct of the trial may restrict their use.

As a company progresses through the clinical research process, an optimal dosage strength (or strengths) is discovered. This fine-tuning is accompanied by a minimization in the number of different strengths of clinical product required.

As per our previous example, phase II dosing may only require placebo, 25 mg, and 100 mg entities to dose placebo, 25 mg, 50 mg, 100 mg, and 200 mg groups. Phase III may include dosing of 100 mg (and a matching placebo).

The placebo usually is not a major consideration in this process; however, a decision needs to be made as to whether a true placebo (excipients only from the active product) or a "universal placebo" is used. Since all of the efforts in making a placebo batch are similar to those for active drug lots, it may be beneficial to manufacture a single lot of 1 million placebo capsules to use in multiple investigational programs. Of course, each time the universal placebo is used, QC must perform an identity test for the absence of drug substance for the specific program. It is still time-saving for the manufacturing group even though other groups have some minimal work to perform.

The choice of excipients in the universal placebo must be contemplated. Lactose is a possibility, but its use in gastrointestinal programs may be prohibited. Not every clinician or regulatory personnel may agree to this concept, but if accepted, it will save valuable time in the long run.

Also noted in the bulk request form is the comparator drug(s) that will be required in the clinical program. Unless the investigational drug is a "first-of-a-kind" therapy, the FDA will require that the investigational drug's efficacy and safety be compared to that of a current market leader in phase II or III. Once the comparator drugs are identified, considerable effort needs to take place. Several choices become evident, the first of which is to request the comparator (and matching placebo) from the innovator company. Several years ago, the Pharmaceutical Manufacturer's Association (PMA) produced a series of draft guidelines, both for the requester and requesting companies. The ac-

tions of many companies must be lauded for honoring the spirit of the PMA guideline; all companies will have to go through this exercise. By obtaining the comparator drug from the innovator, many bioequivalence and/or manufacturing issues disappear (these issues will be discussed shortly). Identification of the comparator drugs needs to be performed to allow for several actions to occur. The innovator needs to see a copy of the clinical protocol to ensure that the comparator will be used within current market labeling. Of course, development of a complete protocol at a very early stage is difficult; many companies will accept a draft protocol or abstract. Review of the protocol/abstract may take a considerable amount of time within the innovator company. The liaison must be able to coordinate such activities even though it is never a priority to assist a competitor company. Approval of the protocol must be from any or all of the following groups: (a) R&D Pharmaceutics/Analytical, (b) Clinical Research, (c) Finance, (d) Regulatory Affairs, (e) Marketing, and (f) Legal. Approval of the provision of the comparator drug may be unconditional or conditional. If conditions are set, they most likely include reciprocation of some sort. Normally, the reciprocation entails the provision of another comparator drug in return at *some time*. Companies may hold this return "promise" at a time that is less than optimal. This is one of the reasons that legal departments are involved to produce a "fair" contractual agreement. Finance must be able to price the product and also the matching placebo. Strategic Marketing must determine whether providing the comparator jeopardizes the "franchise" in any manner. Medical and Regulatory Affairs personnel are approving the use of the drug as noted previously; they will also request the privilege of reviewing the data after the clinical trials have concluded (provision needs to be included in the aforementioned legal agreement).

Since the original request was for the comparator drug and a matching placebo (to ensure blinding), the two products must be identical and normally without market logo evident. Assuming quantities are normally not large, the work will be performed by the R&D Pharmaceutics group, with analysis by the R&D Analytical department. These departments are not anticipating such requests from outside companies; therefore, the manufacture and analysis must be worked into other internal priorities.

By the time (a) the draft protocol/abstract is provided, (b) meetings are held to determine the acceptability of the request, and (c) the manufacture/analysis is performed, 6 months or longer may have elapsed. Once again, this is the manner in which to proceed to negate any bioequivalence issues. Also, remember that if the company refuses to honor the request for any reason, it may be labeled as a nonsupporter of the old PMA position or a new PhRMA initiative. Any requests from them may be automatically refused; word travels fast in the pharmaceutical industry.

If the innovator company does not approve the request for the comparator drug, other options must be pursued. For a solid dosage form, there are several possibilities; however, for a prepackaged product (i.e., aerosol, parenteral product) options are very limited.

For tablets and capsules, the simplest approach is to place them in an opaque capsule. To prevent rattling, an appropriate excipient may be overfilled. This approach works only when tablets are sufficiently small to fit into the capsule (usually #00 maximum). By performing an in vitro dissolution test, one can demonstrate equivalence between the original market product and the encapsulated product. A matching placebo could be managed by first manufacturing a placebo tablet with an excipient overfill to preserve the blinding between the placebo and the active. Similarly, market product can be blinded by overcoating it with a water-soluble opaque polymer. Embossed tablets may have markings that may not be coated at 100% efficiency. Placebo tablets should have a "similar" logo that can also be coated to the same efficiency level.

The next option would be to modify the dosage form in some manner. This might involve breaking a tablet in half and placing it in a capsule or milling a tablet and to re-tablet it into another shape or encapsulate the milled product. An in vitro dissolution testing comparison may be performed, but personnel from a drug metabolism group will have final decision-making power. The need for a human bioequivalence trial may be necessary; this additional clinical trial can be performed either before or in conjunction with the intended efficacy trial. The risk is that bioequivalence is not demonstrated.

A third possibility is to actually obtain drug substance from a chemical manufacturer and formulate a product as one would formulate a new chemical entity. Need for a bioequivalence trial is quite probable for this scenario.

In any case, analytical methodology and the associated reference standard are not easily obtainable. Considerable in-house work needs to be performed. If the innovator company does not want to provide the comparator, there is little chance that the company will provide analytical methods or the reference standard.

A true commitment from the pharmaceutics and analytical departments is required for the comparator drug development. In addition, sufficient stability data need to be generated not only to allow for the start of the clinical trials, but also for the conduct of the entire trial. A realistic time frame is once again 6 months. If the work cannot be performed in-house in a timely manner, a viaible alternative could be to use a contract facility.

IV. PACKAGING REQUEST

Normally, bulk supplies are not sent to the clinic; they obviously need to be packaged. As one may expect, whereas the manufacturing group is concerned

about preparing lots or batches of products, the packaging group must take these *bulk* supplies and turn them into a finished pharmaceutical entity, which includes not only the packaging, but also the labeling. It is important to remember that once a finished product leaves the pharmaceutical company, the next person that views the clinical trial supplies is the investigational site personnel (i.e., doctors and nurses) and ultimately the patient. One picture is worth a thousand words, and you don't get a second chance to make a first impression; pharmaceutical elegance is of primary importance when these people are viewing the company's product, which is a reflection on the company itself.

The liaison must coordinate not only the bulk requests for the manufacture of the products but also the study-specific packaging requests. Similar to the example of a bulk request that was presented previously, Fig. 2 is an example of a packaging request form. Once again most areas are self-explanatory; however the clinical study requirements or exact details need to be specified.

A major area of concern is the intended clinical study start date. For several companies, that date has been etched in stone. Investigators have patients scheduled for a specific date; no changes are allowed. For other companies, the study start date is flexible. This should not be misconstrued as a date plus or minus 3 months, but plus or minus 2 weeks.

The liaison must stay in constant touch with the medical group to ensure that the study start (or other requirements) do not change.

One cannot expect that a request is given one day and everything is packaged/labeled ready to go the next day. Normally, standard operating procedures (SOPs) cover the length of time required for study packaging, which depends on the type and complexity of the study. In a healthy environment in an R&D setting, the "pipeline" is full, and multiple studies are being planned and actually packaged for various products in different phases of development.

Single site, short-duration studies (e.g., early phase I, bioequivalence, pharmacokinetic) are fairly simple to plan and package. Multiple site, longer-duration studies (e.g., efficacy, long-term safety) are not quite as easy. For the latter, multiple packaging runs may be required due to lack of drug product (due to lack of drug substance or other reasons) or simply lack of adequate stability data information on how long supplies can be used. The timing for the first packaging job of a series for a single protocol is set as for any other study. Subsequent packaging jobs *must* be performed at definitive times in the future to allow for a smooth transition that is a minimum deterrent for the site and invisible to the patients.

Other types of studies that require a definitive start date are ones for allergy (e.g., start of ragweed, pollen seasons) or upper respiratory (e.g., flu, bronchitis, pneumonia). Also included here is the initial IND clinical study, normally initiated 1 month after the regulatory submission. Action must be taken

Date Submitted: _____ Authorized By: _____

Date Requested: _____ Request No.: _____

Clinical Study No.: _____ Clinical Study Start Date: _____

Study Country(s): _____ No. of Investigational Sites: _____

Foreign Language Study Requirements: _____ Study Duration: _____

Bulk supplies to be used	Bulk Request #	Lot #	Study Type:
Actives _____	_____	_____	open label ___
_____	_____	_____	single label ___
_____	_____	_____	double blind ___
Placebo _____	_____	_____	
Comparator _____	_____	_____	
Comparator placebo _____	_____	_____	

Package Instructions: _____

_____

_____

_____

Assigned to: _____ (Packaging Manager)

Copies to: _____ (Packaging Director)

_____ (Analytical Director)

_____ (Quality Assurance Director)

_____ (Central File)

Date Available: _____

Approved By: _____ Date: _____

FIG. 2. Request for clinical study packaging.

immediately to allow for prompt starts to these studies; however, it is not an excuse for late planning by Clinical Research.

Long-term commitment studies for compassionate use, Investigator INDs and treatment INDs are a common occurrence. Normally, a number of bulk

packages are assembled and shipped on a single day's notice. When an inventory drops below a critical level, a new packaging job is required.

Through previous conversations between the liaison and personnel from Clinical Research, packaging materials are normally specified. Bottles are the norm, but unit dose packages are not. If a unit dose blister is required, sufficient lead time needs to be allowed for procurement of appropriate materials and stability storage/testing to take place. As can be expected, several months for this process is not out of the question. Utilization of tamper-evidence (i.e., induction seal liner) or child-resistant closures are also a possibility.

Obviously the packaging/labeling instructions are critical information that need to be included in this request. Normally, a draft protocol, or worse case abstract, is presented with the packaging request for conformation (or for future revision) of the conduct of the trial.

V. THE PLANNING PROCESS

Prioritization has been described briefly, but a more in-depth discussion is warranted. Normally, workload on a "macro" scale is discussed at management meetings or at project teams. Time lines are discussed for IND submissions, NDA submissions, start of different clinical phases, etc. The liaison, however, needs to work on more of a "micro" scale for bulk packaging and the tie with clinical packaging. Planning meetings may be held on a quarterly basis with the directors of the Clinical Research department. There should be separate meetings with the directors from different therapeutic groups. In addition, meetings should be held with other medical groups (e.g., phase IV operation). Within each group, priorities should be given by New Chemical Entity (NCE) and by a protocol basis. What the liaison then needs to do is collate all of the information and actually present it to either the vice president of Clinical Research or his or her designee to ensure that everyone is on the same wavelength. The best scenario is having the vice president select the overall priority of all the programs/protocols. Normally, however, the liaison is asked to perform this work since this is more of a "micro" task.

Planning must include long-term and mid-term assumptions for bulk drug substance requirements to allow for drug product manufacture of different strengths. Comparator drugs also need to be identified. Normally, long-term and mid-term planning takes 6 to 12 months. No one expects these plans to be permanent. This planning provides only a "ball park" estimate for workload considerations.

Near-mid-term and short-term planning (1 to 6 months) must include final planning for manufacture, including the bulk request at approximately 4- to 6-month time point. Packaging requests should be received 2 to 3 months before the expected ship date.

Tracking documents can be used for this planning process (Table 2): As can be imagined for a "healthy" pipeline, this list may be several pages long, since this not only includes upcoming studies, but ongoing studies. The basic concerns for ongoing studies is for possible resupply due to lack of sufficient stability for products already at clinical sites.

The list must be updated on a regular (preferably monthly) basis to keep the liaison in constant touch with the possible changes for predefined protocols and inclusion of new protocols. The updating process is no simple task, possibly requiring the work of multiple medical and/or data entry personnel.

Sufficient information needs to be included to allow for the planning process to occur. For Study X-108, the drug products have not yet been identified, but the liaison can get a "worst-case" and "best-case" estimate from medical personnel involved in writing of the protocol. By noting that a comparator drug is to be utilized, a search may be started. This protocol should have first been mentioned 6 to 9 months before the expected start date to allow for several different procurement possibilities as noted earlier.

Table 3 provides a summary of what is required in planning for short-, mid- and long-term clinical supply requirements.

VI. INTERNATIONALLY BASED COMPANIES

One of the many reasons that many pharmaceutical companies have both European and U.S. affiliates is to handle the investigational drug supply process in a more efficient manner. Trying to furnish drug product and also conducting the clinical trial in the United States for a European company is quite difficult. In addition, the converse is true.

Many such companies may be able to discover and synthesize drug substance on either side of the ocean. The questions then becomes where to manufacture and package the clinical supplies. There is no right or wrong answer, but certain considerations should be taken into account. Location(s) of the trial is quite important. If the trial takes place in either the United States or Europe, then it may make sense to perform the associated work in the country where the trial is being conducted. On the other hand, a certain group (e.g., the European group) may have more (or sole) experience in the manufacture of the drug product even though the clinical trial will be performed in the United States. In this example, the packaging and labeling may take place in the United States after bulk supplies have been shipped from Europe.

In the best of all worlds, the clinical manufacturing groups in the global company have the same equipment; workloads, therefore, are adaptable. Following this train of thought, SOPs and training procedures will have to be very similar at all sites to allow for adherence to GMP's and to ensure that product is manufactured in a similar manner. Another factor to consider deals with raw

TABLE 2 Monthly Clinical Project Tracking-Supply Log 6–12 Month Window from February 1994

Protocol #	Therapeutic Area #1 Protocol writing	Enrollment	Treatment
Drug X-108	Start: 4/94	8/94	9/94
Title: XXXXXX	Complete: 5/94	8/96	9/96
Comments: Study to be started 8/94; last patient dosing 1/97.			
Number of patients = 100	PK study: no	Countries: US, France, UK	
Study type = double blind	Number arms: 4	Comparator: Yes	
Treatment duration: 4 months			
(and so on for other protocols for Drug X)			

Protocol#	Therapeutic Area #2 Protocol writing	Enrollment	Treatment
Drug Y-107	Start: 10/94	2/95	4/95
Title: XXXXXX	Complete: 12/94	8/95	10/96
Comments: Study to possibly start earlier than 2/95; funding may be denied.			
Number of patients = 25	PK study: Yes	Countries: US	
Study type = open label, double blind	Number arms: 2	Comparator: No	
Treatment duration: 6 months			
(and so on for other protocols for Drug Y)			

TABLE 3 Planning Guideline

	Short-Term (<3 months)	Mid-Term (3–6 months)	Long-Term (>6 months)
Product	X	X	X
Protocol reference	X	X	X
Study title	X		
Route of administration	X	X	
Study design	X	X	
Comparators	X	X	X
Number of patients	X	X	X
Countries	X	X	
Treatments	X		
Duration	X	X	X
Dosage forms	X	X	
Strength	X	X	
Packaging description	X		
Labels	X		
Randomization list	X		

material sourcing. Lactose, Hydrous may be cited in the manufacturing procedure, but Lactose, Hydrous purchased overseas may not comply to the same specifications and, therefore, result in different product attributes. Single vendor sourcing may be the only answer.

Another factor that needs to be addressed is import/export of the drug product. To receive drug product from overseas into the United States, one must be ready to address U.S. Customs issues (i.e., product will need to have, at a minimum, an IND filed). A customs broker service is quite helpful in this regard to ensure a smooth transfer of materials to the destination required. One must also address Temporary Import Bond (TIB) issues. If materials are not used or destroyed in a specified amount of time, money has to be spent to extend the TIB period.

For investigational supplies going from the United States to foreign sites, the FDA was requiring an export authorization in some cases. Assuming there is not a NDA or an IND for the drug product, foreign ministries are required to send an export authorization to the FDA, allowing the shipment overseas. This was a hindrance in the past, but this policy has been relaxed recently.

Provision for foreign label copy may present a delay. If U.S. personnel are providing the label copy for approval and eventually labeled product to several different countries, exact translation and also any regulatory mandated information probably will not be accurate. It is best to have local affiliates approval

or even translate the text. Timing for these possible delays has to be considered when planning clinical study start dates.

VII. INTERACTION WITH REGULATORY AFFAIRS

In addition to interactions previously referred to, the liaison should alert the Regulatory Affairs Department to the start of clinical trials to allow for INDs to be updated and export waiver paperwork initiated. These will help ensure that programs are kept on track.

VIII. LIAISON COMMUNICATION: SUMMARY

Some of the best thoughts on the liaison communication have been presented by Marty Jeiven at The Center for Professional Advancement's seminar on the principles of clinical supplies project management. These include communication with all parties involved; Clinical Research, Formulation, Pharmaceutical Analysis, Clinical Packaging, Quality Assurance, and Management.

The liaison must be able to provide an understanding of the clinical study process to clinical research personnel. They do not need a complete understanding; however, they do need to comprehend the essential points to providing supplies in a timely manner. As has been described, there will be a series of requests for clinical supplies in various stages of progress. Plans change, however, and updates need to be provided. One must be able to plan, communicate the tentative schedule, and observe and report progress toward definite goals (e.g., completion of bulk manufacture, completion of packaging, ship dates). Any modifications should be noted and compared to the original plan. An investigation needs to be instituted to discern the problems, and a new plan may be instituted, if required. This cycle must be continued so that no project/protocol lapses. In many ways, the liaison must be a politician; he/she must be able to inform, negotiate, and educate the clinical personnel. When all information has been presented, the liaison must be able to compromise to develop the best scenario for all parties involved.

In many ways, the liaison is also a public relations specialist. The liaison must attend protocol review meetings so that all clinical supplies details/questions are solved before work is started. Tracking meetings need to be held with Pharmaceutical Development personnel (e.g., Manufacturing, Analytical, Quality Assurance, Stability, Packaging) to provide timely updates on status of all studies. If given the opportunity, the liaison should attend investigator meetings to present a talk (and provide samples for viewing) on the labeling and packaging of the pertinent study drugs, along with any special storage condition or unique handling requirements. Such meetings also provide a perfect opportu-

nity to find ways to improve patient and clinical site compliance. Local discussion groups are also the perfect opportunity to meet with other liaisons and to discuss pertinent topics relevant to clinical supplies logistics.

We have already discussed long-term planning on protocols; in addition, the liaison must be able to build long-term relationships with the medical group. This may involve any or all of the following topics: (a) a training module(s) for clinical personnel to get "hands-on" experience in the pharmacy area related to clinical supplies, (b) orientations for new clinical research associates (CRAs), and (c) refresher courses on a periodic basis for CRAs and directors.

Decisions on the utilization of contract facilities for manufacturing and/or packaging and/or labeling may or may not be the responsibility of the liaison; however, he/she must be able to explain the need for using these services. Lack of in-house resources may necessitate their use. Timing and associated costs may become an issue depending on the study start, assuming no changes are made to the schedule. Another option to deal with overload situations is the use of temporary personnel (who need to be trained) with associated space and equipment allocation. It is always a fine balance between how to handle "peaks" in the clinical supply process as opposed to "normal" baseline work. The liaison can help manage or, at a minimum, assist in this decision process.

To rationalize getting additional resources, the liaison must be able to compare certain parameters over a period of time (i.e., from year to year). There is no right way to identify these parameters; they depend on what works best for the specific company. Among the best "measures for productivity" are the following:

1. Requests for Clinical Supplies. This must include not only bulk manufacture requests but also packaging/labeling requests. This may not be the best choice because the work involved for a request for a phase I study is nowhere near the work for a phase III trial. Open label studies are much simpler to plan than double-blind crossover studies, and bottles are easier to read than blister cards. Requests per se do not tell the entire story.
2. Batch Number Assignment. This is similar to the first measure. The manufacture of a batch of 1,000 placebo capsules is not going to be as complicated compared to that of a 100,000 tablet batch that needs to have a granulation prepared and the tablets film coated.
3. Dosage Units Manufactured. This is self-explanatory and provides a good handle on clinical manufacturing workload.
4. Clinical Shipments/Shipping Weight. These parameters do provide a somewhat better handle on work performed. It does not tell one how complicated the study was in setting the packaging or labeling scheme.

5. Labels Generated or Number of Patients Packaged For. These are probably the best resources to link work performed and productivity for the clinical packaging group. Each bottle/vial needs to have a label. In addition, each patient kit or investigator shipment needs labels to be generated and applied.

In summary, there may not be any one true indicator of increase in workload. A combination of some or all of these really gives a true indication of trends in workloads. It is helpful to have more than one indicator to balance the statistics as required.

IX. BENCHMARKING

The liaison within a company may be restricted by company policy, resources, timing, etc. in performing their work. To understand more fully the range of current practice within clinical supply groups, benchmarking exercises are quite useful. By gaining certain insights to what other groups are doing, certain leverage may be applied in-house by noting these practices. If readers would like to take time to complete the following questionnaire, I would be more than willing to tabulate and offer the results to the respondents. The questionnaire was developed by Dr. Subramaniam Shastri.

Resources Organizational Scope:

1. Scope of responsibility, staff strength, facilities layout.
2. Do you have a separate clinical supplies group for manufacturing and packaging?
3. Range of packaging operations and dosage forms.
4. Have you felt pressures to reduce your operating cost? If so, has your firm considered going off shore to reduce operational costs for clinical supplies or other research areas?

Output/Productivity Measurement:

5. How is output measured in manufacturing: by work requests, dosage form units output, batches? In packaging, by number of work requests, operations, sites, studies, or units packaged? How do you treat resupplies?
6. How is productivity measured? e.g., by cycle time, number and volume of batches or units processed/packaged, per cent of batches made successfully first time, percent of studies meeting the client's need date deadline etc. Does resource come up as an issue in discussion of operational efficiency, even if it is only a small portion of the total dollar effort for clinical trials?

Materials Control:

7. Is there a formal planning group or function? Is your scheduling manual or automated? Is it dynamic or updated on a periodic basis for distribution?
8. Is availability of active drug raw material a significant rate-limiting step in the overall clinical supplies availability train?
9. How do you manage your comparator drug requirements need? Do you go to the innovator firm, or do you purchase the product and manipulate it in a variety of ways to blind it? Whose budget carries it?
10. How often do you have to negotiate need dates with your clients? Is that an accepted practice and looked upon with favor by management?
11. Do you manufacture/package to a plan, to a specific request, or to an inventory ceiling and floor levels based on historical data?

Manufacturing:

12. Do you have a Master Batch Record system describing manufacturing and inspection requirements?
13. Work order requesting process: How does the formulator-clinician interaction fare? Who decides whether or not to place a new bulk work order? Is clinical manufacturing actively involved, or is the ball carried by formulators through bulk product manufacturing phase? Do you often have joint purpose clinical supplies/registration batches? If you have a separate clinical processing group, how well are the roles clarified for formulators and the processing personnel?

Packaging:

14. Packaging system: Is it site specific, modular, by job, per shipment basis? Inventory management: How are packaged and labeled supplies inventoried? Charge-in/Reconciliation/lot tracking procedures: Are they automated? Is inventory on-line, manual, or semiautomated?
15. What specifications are used for primary packaging components? Are phase III and commercial requirements equivalent?
16. Accountability limits: Are yields monitored during packaging?
17. Does packaging see the study protocol? At what stage? Does it influence its packaging design content?
18. Label preparation: Who designs the master label? What kind of printer? Are multiple study labels printed at one time? How are patient identification numbers printed? How are labels checked for accuracy and precision before issuance for use?
19. Containers: Do you have standardized containers and filling patterns for packaging? How are materials staged? How are blister cards filled? How are capsules and tablets filled into bottles? How are contents checked?

20. How are patient labels and packaging materials assembled? Manual, automatic?
21. Do you assure complete approval on bulk product documentation before packaging?
22. How is packaged material inspected? Visual, Physical, Chemical ID. What types of sampling plans are used? At what frequency, interval, and level of confidence? How much is QA involved? Is it done across the board for all packaging operations?
23. How are "routine returns" handled? Do you reuse unopened shipments of returned goods from the field, particularly if it involves an expensive product? If so, what tests are required? Beyond what period of time do you destroy returned goods?
24. How many release stages do you have from bulk manufacturing through final packaged product? Which group does the review and release? Do you experience a need for considerable batch documentation "clean-up" to assure total GMP compliance?
25. To what extent is contract packaging used by your firm? Is it mainly for overflow?
26. Do you have bar coding in your packaging operation? If not, have you considered it?
27. Are study retains kept for each regimen? How long are they kept beyond study life?

Stability:

28. Do you conduct stability on all lots? If selective, how do you arrive at the schedule? Do you have expiration dating? When do you stop stability on a lot? Based on a set time limit, e.g. 3 or 5 years or, study completion dates?
29. How do you assure that studies in progress are continuously monitored until the last patient's dosing is completed?
30. Do you have a dedicated QC analysis group to support clinical supplies manufacturing and packaging effort?

Validation:

31. Do you have set validation procedures for equipment, manufacturing, and packaging operations?
32. How large is the scope of your validation effort (i.e., resources employed, and the breadth of operational coverage: e.g., does it extend to packaging)? To what extend do you test and validate each equipment for each product and process including for cleaning process? How does it affect your scheduling program?
33. Is facilities monitoring done across the board in your clinical manufacturing and packaging operations?

QA:

34. What is the level of QA involvement in your operation? Do you have a separate QA group within Research (e.g., who handles line opening and closing, MBR review, batch non-conformance issues, periodic drug product review, master draft label review, specifications review)? What types of control procedures are used to prevent product/labeling mixups of multiple dosages and multiple patient treatments? Do you distinguish between QC and QA in R&D? How many QA personnel are devoted to the clinical manufacturing and packaging effort?
35. How does your internal audit process work? Who is responsible for that? At what frequency? What impetus exists to correct operational deviations after they are identified by audit?

Regulatory/Compliance:

36. What incentives do you use to promote compliance-related discipline among personnel, e.g., freedom for operational errors, documentation errors, facilities, maintenance under state of control at all times?
37. Does clinical manufacturing write development reports?

X. SUMMARY

This chapter has presented a brief view of the overseeing/management of the clinical supply process. Certain areas have been discussed more fully throughout other chapters in this book. The overall thought is that the procedures are simple in theory; in-depth/constant management of each area is required to ensure that time lines are met to comply with company objectives and goals.

8

Clinical Supply Manufacture

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I. LINKAGE BETWEEN CLINICAL SUPPLY MANUFACTURE AND NEW CHEMICAL ENTITY DEVELOPMENT

A. Early Clinical Formulations

An integral link exists between manufacturing clinical supplies and product development. To be successful, it is essential to get New Chemical Entities (NCEs) to humans as quickly as possible. To make efficient use of the development resources (personnel, drug substance, and facilities) a balance must be reached between filing a simple phase I Investigational New Drug (IND) formulation that can be taken into the clinic quickly and developing a formulation that offers flexible manufacturing and robustness that could be used throughout the phase I/II program. To make a balanced decision, one needs to consider the therapeutic class, type of NCE, and medical plan. NCEs that are classified as life-saving medicines such as those used to treat cancer and AIDS may enter phase II and III relatively quickly, requiring larger batches of clinical material in a relatively short period of time. Compounds in this category have received approved New Drug Applications (NDAs) after phase II trials have been completed. In our experience, development of life-saving medicines requires the formulation scientist to place more effort in the early clinical formulations with the idea of establishing a "final product" by phase II pivotal studies. To meet this aggressive time line, many formulation/process studies are done in parallel with the clinical program.

For purposes of this discussion, NCEs can be classified into novel therapeutic breakthrough compounds or follow-on compounds. Both types offer significant advances in medical treatment, but the clinical development programs may differ significantly. The medical program for a breakthrough compound carries a high risk of failure and may not justify the allocation of large resources and time to develop a robust clinical formulation for the initial clinical trials. It is usually more critical to get the medicine into humans to test the breakthrough hypothesis, which may be accomplished with a very simple clinical formulation and process.

Usually there is much more information known about a follow-on compound. The mode of action, drug safety, and medical programs are better defined; and companies are willing to allocate more resources to a follow-on compound to accelerate the clinical and development programs. In this case, it is more desirable to develop a clinical formulation that will support the phase I program in its entirety.

Ideally, it is desirable to develop a simple, easy to manufacture formulation that can be used throughout the phase I and II clinical trials. While the clinic is being supplied with the phase I formulation, parallel development efforts can take place to develop a "final product" for phase III clinical trials and the NDA. This ideal scenario depends strongly on what level of risk the cor-

poration is willing to take and the opportunity costs associated with investing this level of resources early in the development process. In general, companies are more willing to risk resources on a follow-up compound, which is expected to offer therapeutic advantages.

Extemporaneous compounding of an NCE at the clinical site is the quickest way to test the NCE in humans. This approach is most reasonable for breakthrough compounds where early experience in humans is critical. However, one needs to be prepared to meet larger clinical supply requirements quickly if desirable results are seen in the early human studies. The use of a sterile parenteral dosage form offers many advantages for first time in human studies. A sterile parenteral dosage form:

- Can be manufactured in larger scale while minimizing material requirements.
- Eliminates many absorption and bioavailability questions that may arise by administering the drug orally.
- Offers a high degree of dose flexibility with minimal dosage strengths, which minimizes typical compound manufacturing loss and the related manufacturing resources.
- Provides a relatively inert contact material in the case of a glass ampule container/closure system.

If the initial studies require quantities that cannot be easily manufactured extemporaneously, these advantages may be offset by the need to validate the sterile manufacturing process, which is also time and resource intensive.

Handfilling capsules or manufacturing tablets on a single punch table machine may provide enough supplies for the clinic to allow time to develop a more automated process. In any case, it is cost effective to make the largest possible batch because the support resources required to write the batch record, approve the batch record, provide manufacturing support, perform in-process testing, release testing, stability testing, and obtain quality assurance approval requires the same level of effort regardless of the batch size.

B. Formulation and Process Development

It is preferable to develop a formulation that can be used throughout phase I. While this formulation is used to supply the clinic, a "final product" that defines the formulation and process can be developed without affecting the medical program needs or timing. The authors have been able to develop simple phase I formulations (four component direct compression tablets, four component oral liquids, and three component parenterals) that have become the NDA formulations by applying fundamental preformulation and formulation considerations to the selection of the first clinical formulation.

The decision to manufacture clinical supplies carries significant resource implications, which can be referred to as the "clinical manufacturing resource multiplier effect." Formulation development personnel, pilot plant staff, quality assurance, quality control, validation, and other support functions need to closely coordinate their activities and responsibilities. Material that is used for clinical manufacture will need to be replaced by the chemical pilot plant, which imposes further personnel and cost requirements.

The following suggestions are given to minimize the clinical manufacturing resource multiplier effect. It is important to establish an early dialog with the medical department to understand the desired outcomes of the medical program. By understanding the medical needs, it is possible to mutually agree to minimize the number of dosage strengths and provide the most dose flexibility (e.g., use of liquid or injectable). A stable formulation can significantly reduce the resources required to maintain supplies in the clinic. The clinical formulation should have at least a 1 year shelf life at the specified storage condition. A 1 year shelf life would result in clinical supplies being manufactured every 8 to 10 months if one assumes that it would take 2 months to manufacture and release bulk supplies, package and label the clinical material, and ship the supplies to the clinical site. The number of dosage strengths and placebos also will affect the manufacturing lead times. A stable clinical product and an accurate supplies forecast allow larger batches to be manufactured, which provides for optimal use of the available resources. Decreasing the total number of batches manufactured also decreases the overall amount of drug substance that is used for release testing, in-process testing, and stability testing. Manufacturing loss will also be decreased. In general, developing stable clinical formulations that offer dosage flexibility and minimize manufacturing loss will reduce the clinical supplies resource multiplier effect.

The formulation and process development activities directed at finalizing a commercial product can occur in parallel while the clinical inventory is maintained to support the medical program. Since only one out of four or five compounds that enter phase I is actually commercialized, the risk and timing of starting significant formulation and development efforts need to be carefully evaluated. Once a decision is made to initiate full development, significant company resources are committed, which requires sufficient compound and analytical support. It is desirable to have the "final product" defined by the start of the pivotal clinical studies. For medicines that are categorized as life-saving, it is possible to submit an NDA at the end of phase II, which requires that the formulation development work and clinical manufacture efforts be accelerated.

The linkage between formulations used in early clinical studies, the pivotal clinical studies, and the commercial product is also a frequently asked regulatory concern. The goal of many companies is to finalize the commercial

product (formulation and process) for the pivotal clinical studies. To develop a commercial product to be used in the pivotal clinical studies significantly compresses the development time. One way to compress the development time, while maintaining a quality development program, is to perform formulation/process optimization and scale-up studies in conjunction with clinical supply manufacturing campaigns.

C. Formulation/Process Optimization and Scale-up Studies

Oftentimes there is a shortage of drug substance, and it is not uncommon that the first opportunity for a formulation scientist to scale-up the formulation/process is when the clinical supply requirements justify the need for larger batches. The formulation scientist can incorporate carefully designed studies around the clinical batch to identify critical formulation component and formulation variables. For example, the bulk drug and excipient particle size distribution, surface area, melting point, bulk/tapped density, hygroscopicity, and static charge properties could all be critical to the scale-up and transfer of a solid dosage form. Characterization and control of such variables often play a key role in minimizing difficulties in manufacturing clinical supplies as the scale is increased. The effects of formulation variables, in particular the levels of excipients on the product characteristics, should be ascertained early in the development to minimize difficulties in manufacturing the different strengths of clinical supplies. In the case of a solid dosage form, lubricant, disintegrant, and binder levels should be studied and ranges established.

By using equipment with similar operating principles, critical process variables and ranges can be identified and translated to scale-up while meeting the increasing clinical batch sizes required for phase III. Critical process variables are defined as those variables that affect key product characteristics. Key product characteristics for a particular solid dosage form could be dissolution, potency, and content uniformity.

This information serves a dual purpose. Enhanced understanding of the critical formulation and process parameters will result in a more robust product, which allows clinical manufacture to proceed smoothly and efficiently. In addition, the formulation/process and scale-up information develops the link between the clinical supplies used in the medical program and the product that will be transferred to production.

II. PROCESS VALIDATION

Process validation for clinical supplies differ slightly compared to production process validation (1). Manufacturing processes for clinical supplies are often not repeated. A process may be implemented only once before a change in

scale, equipment, or process variable is implemented. The usual product validation scenario of performing process validation on three or more identical batches is often not feasible in clinical manufacturing. To ensure the quality of eash batch, it is acceptable practice to collect sufficient in-process data to guarantee the quality.

Data collected from the formulation/process optimization and scale-up studies can also be used to show that the process is understood and reproducible. In addition, sufficient in-process data can be collected during the actual clinical manufacture to ensure that the process does what it purports to do. This combination of experimental and clinical manufacturing data may be used to ensure the quality of the clinical batches.

III. FACILITY AND EQUIPMENT NEEDS

It is ideal to have a pilot plant that is designed to support product development activities and clinical supplies manufacture in a current good manufacturing practices (cGMP) compliant environment (2). The very nature of product development starts with many unknowns that eventually, through well-designed development programs, result in a value-added product. Because of these unknowns, it is difficult to predict a priori the physical facility requirements; thus there is a need to incorporate as much flexibility into the facility design as possible.

Efficient clinical supply manufacture also requires a wide range of equipment sizes, preferably of identical design so that critical process information can be gained while increased clinical program requirements are being met. Clinical supply demands increase quickly from a few hundred units to several million. Tablet batch sizes in the authors' pilot plant have ranged from 80 g to 400 kg; liquids from 0.5 to 600 liters; aerosols from 1 to 200 kg; creams/ointments from 1 to 300 kg; and sterile products from 1 to 200 liters. The larger batches sizes are not uncommon, especially for phase III and postapproval programs. Companies that do not have a pilot plant capable of handling these larger batch sizes often use their production facility or a contract manufacturer. In these cases, one forfeits a degree of flexibility, which may result in clinical programs being delayed. Having control over the clinical manufacturing facility gives more flexibility and usually results in shortened turnaround times. It is critical to be able to respond quickly to changes required by the medical group, Food and Drug (FDA), or unexpected manufacturing demands.

The generic drug division's ruling on batch size requirements also makes it important to be able to manufacture clinical supplies and stability batches on a larger scale. Currently, for solid oral dosage forms, biobatches are to be manufactured at least one-tenth scale of the planned commercial batch size or minimum of 100,000 dosage units (3).

Clinical supplies must be manufactured under cGMP. To be cGMP-compliant, the facility also needs to have proper support staff and functions to provide training, validation, maintenance, calibration, engineering, microbiological/environmental monitoring, warehousing, dispensing, housekeeping, quality assurance, and quality control. These operating costs run into the millions of dollars and should be factored into the cost of manufacturing clinical supplies.

IV. OCCUPATIONAL HEALTH, SAFETY, AND ENVIRONMENTAL CONSIDERATIONS

A. General Health and Safety

General safety considerations should meet federal, state, local and corporate fire and emergency requirements. Consideration should also be given to the manufacturing process and equipment being used. Explosion proofing, venting, static grounding, and containment options are typically process and technology driven. Handling potent compounds or compounds that have minimal information regarding potential toxicity, potency, and physical chemical properties requires special precautions.

B. Potent Compound Handling

Depending on the potency and pharmacological class, there may be a need to perform the manufacturing in an isolatable area that protects both the personnel and the environment from the compound. This may require the use of specific engineering controls to prevent cross-contamination and exposure of personnel in other areas of the facility. Provisions may require powered air breathing units or breathing air suits and decontamination showers. Routine blood testing may be performed to confirm that adequate safety measures have been taken.

Several companies have established a matrix classification system for determining the level of containment required for a particular class of compounds. Many companies rely on the expert advice and assistance of occupational hygienists, physicians, and engineering staff to provide professional recommendations regarding the safe handling of potent compounds. Evaluation of the unit operations and process chain may require the manufacturing processes to be modified or changed completely. Processors that minimize dusting and transfers, and allow initial "rough" cleaning to be done in place are desirable. Processors such as microwave/granulator/dryers or vacuum/granulator/dryers offer many of these advantages. Liquid and suspension dosage forms also minimize potential airborne contamination. Semisolid capsule fills or soft gelatin suspension or liquid fills also result in less risk of airborne contamination. When

potent compounds are involved, it is desirable to perform routine environmental monitoring. It is also important to assess the environmental effects that the compound may have and to set up appropriate waste handling procedures (4).

V. CLEANING VERIFICATION/VALIDATION

A. Verification vs. Validation

As a result of any typical pharmaceutical process, a residual level of the drug substance remains on equipment and facility surfaces after clean up. This residual drug potentially may be carried over into the next product, resulting in adulteration of the second product. For this reason, cleaning methods are developed that consistently lower the level of drug residuals to a level that is deemed acceptable. In a production setting, the cleaning methods are typically validated. However, in early product development and clinical supply manufacture, validation of cleaning methods is impractical and in many cases impossible. This is due to several reasons. Most companies will rarely manufacture the three required batches of the same formulation, utilizing the same process and equipment during the early phases of development. In addition, it is common practice to use the same facilities for early experimental compounds and clinical supply manufacture. Finally, the sheer number of compounds handled in a multiuse development facility makes cleaning validation impractical. To cope with this situation, most pharmaceutical development organizations either (a) group similar equipment and products (based on the compounds solubility, structural similarity, dosage form composition, potencies, and degree of cleaning difficulty) together or (b) perform cleaning verification rather than validation (5).

Cleaning verification is a process in which the residual drug substance levels on equipment and facility surfaces are measured at appropriate intervals and compared to predetermined specifications. Some companies may verify cleaning after each batch of product is processed, while other companies verify cleaning only before a clinical manufacturing batch. If the facility and equipment are multiuse (experimental development and clinical supplies manufacture), the cleaning verification procedure must be flexible enough not to impede experimental work while still ensuring the integrity of each batch of clinical supplies. Although cleaning verification of facility surfaces is occasionally pursued for highly potent compounds, many companies forego facility surface testing. The rationale for this is that the facility surfaces are not product contact surfaces, and residual levels of 1 to 4 $\mu g/cm^2$ are visible for most compounds (6,7). This level of contamination on a nonproduct contact surface represents an insignificant risk of carryover to the next batch.

B. Sampling Methods

There are significant discussions in the literature concerning the optimum method of sampling residual drug substance levels (5). The two most widely used methods are physical swabbing and solvent rinse testing. Physical swabbing works well for equipment or surfaces that are smooth, easy to reach, and readily visible. The levels of drug substance detectable using swabs depend on variables such as the surface area swabbed, the suitability of the solvent used to wet the swab, the extractability of the drug substance from the swab material, the degree of force used in swabbing, and the specific area swabbed. Each of these variables must be adequately addressed to ensure the reliability of the swab results. Physical swabbing does not support a comprehensive evaluation of equipment surfaces, and its usefulness is especially limited for equipment that has piping and inaccessible product contact surfaces.

The solvent rinse testing method also has variables that must be controlled. They include the effectiveness and quantity of solvent used, the contact time of the solvent and test surface, and the volatility of the solvents. The solvent rinse testing method has the primary advantage of covering more of the equipment surface. Perhaps the best choice of sampling is actually a combination of solvent rinse testing and physical swabbing in conjunction with a thorough visual examination. This combination approach allows the development scientist to determine whether the residual contamination is uniform, sample any obvious "dirty areas," extract residuals from cracks and crevices, and rinse out any closed loops or piping.

C. Setting Residual Limits

At least four basic methods are used to set limits for residuals: (a) limits based on lowest clinical dose, (b) toxicity (no-effect dose), (c) batch carryover (dilution factor), and (d) cleaning capabilities (6). Each of these methods has specific attributes and advantages that match the cleaning requirements for specific products and specific phases of drug development. Unfortunately, the information required to rationalize and develop residual limits using some of these methods is not available for phase I and II clinical supplies. A limit based on the lowest clinical dose, divided by a standard safety factor (1000) provides an adequate specification for most compounds when coupled with a "no visible residue" clause. In some instances, this should be further refined to account for the specific surface area tested and the total surface area of the equipment. As development progresses towards product transfer, a more refined and specific specification can be initiated. This is especially true once the intended manufacturing equipment is selected and final toxicology data are analyzed.

VI. COMPARATORS

A. Definition

Comparators are positive control active drug supplies. Their therapeutic activity during a clinical trial essentially validates the study and establishes the base line for efficacy with which to measure (or compare) the drug under study. As regulatory agencies increasingly demand superior performance from new drugs under development, the proper use of comparators to demonstrate superior performance is crucial. Comparators may be used in their market image and package for open labeled studies. However, for blinded clinical studies, the identity of the drug is not disclosed (blinded) to the patient and/or the investigator.

Typically, the clinical research management responsible for the design and implementation of the study selects the comparator. The selection process historically has included input from marketing and medical groups. More recently, in an effort to accelerate the drug development process, marketing and medical have included the development scientist as a partner in the decision process. The development scientist is ultimately responsible for developing and manufacturing the clinical dosage forms and can evaluate the ease and speed with which a comparator can be produced. If the medical and marketing considerations are essentially the same, comparators that are easier to blind or do not require extensive development time are chosen over more difficult products.

B. Blinding of Comparators

To avoid bias in the clinical program, clinical dosage forms are "blinded." Blinding is a manipulation or manufacturing technique that renders different drugs and placebo indistinguishable from each other. Ideally, the NCE, comparator product, and placebo product look, feel, and taste exactly the same. The market image of the comparator must be concealed (blinded) since manufacture of a matching placebo with the marketed trade dress is considered misbranding.

If the NCE is a different dosage form than the comparator, a double dummy approach is used. A double dummy study utilizes two different placebo products—thus the name. For example, if the NCE product was a tablet and the comparator was an oral liquid, the comparator would be blinded and matching placebos of both products would be developed. The patients in the clinic would then receive either NCE tablets and placebo liquid or active comparator liquid and placebo tablets. In both bases, neither the patient nor the clinician would know which active drug was being administered.

Methods of blinding depend on the dosage form, physical and chemical characteristics of the drug product, level of "blinding perfection" desired,

quantity of clinical supplies needed, and potential manufacturing processes. Typical blinding techniques for tablets and capsules are shown in Table 1. Blinding techniques for other dosage forms are shown in Table 2. Each technique requires standardizing certain critical parameters to ensure the dosage forms remain blinded to the patient and the clinical investigator. It is important to note that blinding of metered dose inhalers and powders for reconstitution is especially difficult. For these dosage forms, a balance must be reached between "practical blinding" and what is technologically feasible. For some of these blinding techniques, modified or specialized equipment may be required.

C. Sourcing Comparators

It is most desirable to obtain comparator supplies from the innovator. Obtaining blinded comparator supplies has many advantages over internal development. These include the assurance the supplies will meet the regulatory requirements, be bioequivalent to the marketed product (provided the innovator did the required development work), and eliminate the need for dedicating internal resources for manufacturing and release. In addition, the cost of purchasing the comparators will almost certainly be less than internal development. However, most pharmaceutical companies will insist on reviewing the draft clinical protocol and will require a comprehensive legal contract and reciprocal agreement to receive blinded supplies of interest for possible future studies. In addition, they may insist on reviewing the clinical study summary before submission to regulatory agencies or publication in the clinical journals. Each of these issues requires thoughtful consideration on the parts of both companies. Reaching an agreement can be time consuming. Purchasing comparators is the best solution if the disclosure of the technical details of the clinical study is not an issue and the study start date is neither imminent nor critical. Most innovator companies diligently analyze the potential repercussions of such transactions before agreeing to supply their clinical products. Adequate forward planning is required to provide enough time to effectively negotiate these agreements. Some informal surveys suggest that the majority of pharmaceutical companies actively pursue sourcing blinded comparators directly from the innovator before initiating an internal development effort. Realizing the potential difficulties of these negotiations, some companies exclusively choose internal development while other companies pursue both avenues simultaneously. It is advisable to establish an internal "drop-dead" date at which time negotiations are terminated and internal development of the blinded comparator is begun. Fig. 1 contains information that is useful to the requestor and supplier of comparators.

D. Development of Comparators

Development of blinded comparator dosage forms is very similar to NCE de-

TABLE 1 Common Blinding Techniques for Tablets and Capsules Correlated with Critical Blinding Parameters, Equipment Types, and Associated Testing Requirements

Blinding method	Critical blinding parameters	Common equipment utilized	Testing requirements
Overencapsulation of intact tablet or intact capsule	capsule appearance capsule weight capsule shell integrity	Elanco Fil Parke Davis Rotoweigh or Mocon (check-weighers), MG-II Futura	comparative dissolution stability testing
Film coating of tablet or capsule (obscures printed logos and color)	tablet or capsule appearance	Film coating pans (Vector, Thomas, Glatt)	comparative dissolution stability testing visual—matches placebo
Overencapsulation of broken tablet (scored tablets)	capsule appearance	Holland-McGinley Tabcap (breaks tablets)	comparative dissolution
	capsule weight capsule shell integrity	Bonapace Elanco Fil Rotoweigh (checkweigher)	content uniformity stability testing
Milling of tablet and encapsulation of powder	capsule appearance capsule weight capsule shell integrity	Elanco Fil MG-II Futura Parke Davis	bioequivalency test content uniformity (of powder and capsules) stability testing

Milling of tablet and recompression on standard tooling	tablet appearance tablet weight tablet thickness	Quadro Comil Fitzmill (Knives Forward) other low shear mills any compression machine	bioequivalency test content uniformity (of powder and tablets) stability testing visual—matches placebo
Removal of printed logos	tablet appearance tablet color/gloss	Coating Pans	residual solvents comparative dissolution stability testing visual—matches placebo
Encapsulation of tablet or capsule granulation	capsule appearance capsule weight	MG II Futura Elanco Fil Parke Davis	comparative dissolution content uniformity (of powder and capsules) stability testing
Sugar coating to obscure engravings	overall appearance tablet shape uniformity of sugar coat	Coating Pans Thomas Accela Cota	comparative dissolution visual—matches placebo stability testing

Note: 1. For critical studies, bioequivalency testing should be considered in all cases.
2. All techniques typically require the development of a matching placebo dosage form.
3. Overencapsulation of a bead-filled capsule may necessitate a bead-filled placebo to match the rattling sound of the active product.

TABLE 2 Common Blinding Techniques for Liquids, Powders, and Metered Dose Inhalers Correlated with Critical Blinding Parameters and Associated Testing Requirements

Blinding method	Critical blinding parameters	Testing requirements
Powder for Reconstitution		
Repackage product and produce	powder color	extensive physical testing (placebo only)
	powder texture	stability testing (active and placebo)
OR	particle size	
	fill weight	
	smell	
	taste	
Remove/cover product labeling and produce matching placebo in identical container closure system	ease of reconstitution	extensive physical testing (placebo only)
	reconstitution volume	stability testing (placebo only)
	viscosity	
	color stability after reconstitution	
	physical stability of suspension	
Liquids		
Repackage product and produce	color	stability testing (active and placebo)
	clarity	
OR	viscosity	
	taste	
	smell	

Remove/cover product labeling and produce matching placebo in identical container closure system	identical placebo packaging	stability testing of placebo only
Metered Dose Inhaler		
Remove/cover product labeling and produce matching placebo	overall appearance identical actuator identical canister identical valve matching powder residue for placebo canister pressure fill weight actuation sound taste	appearance leak rate shot weight microbial limits test

Note: All techniques typically require the development of a matching placebo dosage form.

Requestor

Drug, dosage form, potency
Size, shape, color, coating, etc.
Quantity (including overage)
Date needed
Test procedures for final dosage form or agreement from supplier for same
Compliance with local, U.S. and foreign laws applicable to use of the material
Liability and indemnification statement approved
Agreement from requestor to reciprocate
Copy of study protocol or the following minimal information:

- Study title and objective
- Study design
- Patient inclusion and exclusion criteria
- Dosage(s), duration(s) of treatment and drug administration
- Number of patients in study
- Countries where study will be conducted
- Description of labeling and packaging
- Intended use of overage

Supplier

Method and timing of payment
Limits on use of requested material
Will requestor provide samples of any modified dosage form?
Availability of study results and prepublication manuscripts
Letter authorizing FDA to reference suppliers IND/NDA on requestor's behalf
Certificate of analysis with reassay/expiry date for requestor's packaging
Material safety data sheet for drug
Review protocol
Resolve reciprocity issues

FIG. 1. Information typically needed when purchasing/supplying blinded comparators.

velopment programs. The primary differences are that the comparator program is somewhat abbreviated and on a compressed time line. The development of blinded comparators is outlined in a flow diagram (Fig. 2). Typically, development starts with an assessment of potential blinding techniques and an evaluation of the risks and impacts of each technique. The formulator should strive to minimize the potential risk of producing a blinded dosage form that does not perform exactly as the initial comparator product. The most obvious concerns are that the blinded product may be less stable, has faster or slower dissolu-

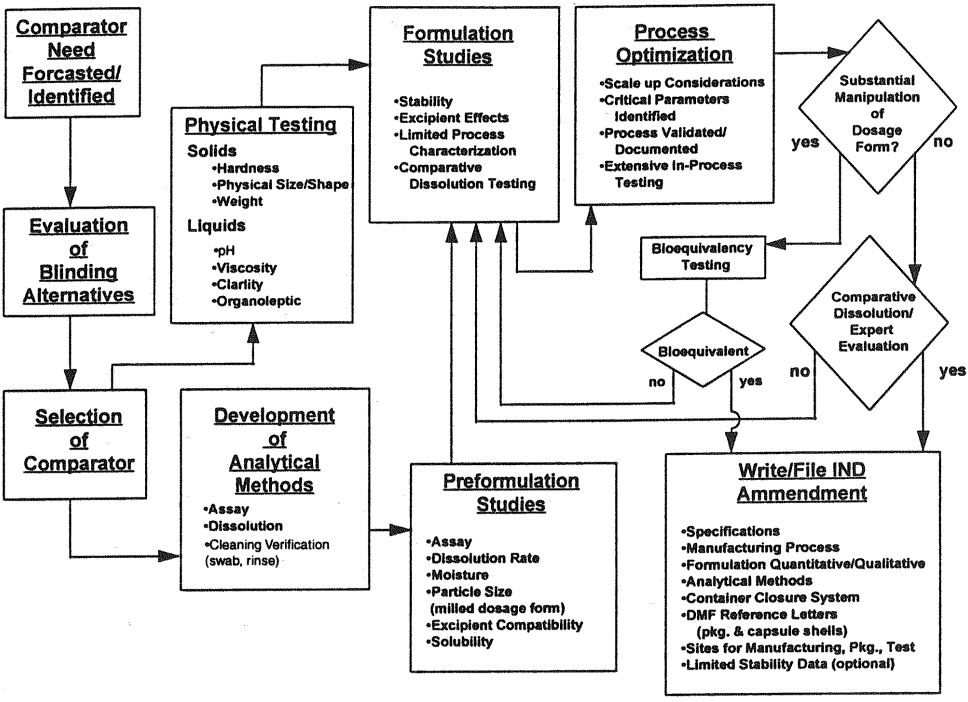

FIG. 2. Flow diagram outlining the development of blinded comparators.

tion rate, or may be more or less bioavailable than the innovator product. The formulator should ultimately choose the blinding technique that requires the least amount of manipulation, maximizes the potential to manufacture a bioequivalent and stable product, and adequately blinds the clinical dosage form. If the comparator dosage form must be manipulated (e.g., milled, overcoated, overencapsulated), the next development step is to initiate preformulation studies. These include, for example, testing of the comparator for assay, dissolution rate, moisture, particle size, hardness, physical size and weight (for solid dosage forms), and accelerated excipient compatibility studies. The results of these studies will aid in the selection of any needed excipients and provide direction during the formulation development process. Many companies forego the excipient compatibility studies if the excipients in the comparator formulation are available in literature such as the Physician's Desk Reference. Although this is a common practice, the lack of detail in these references regarding such factors as the excipient grade, morphology, or hydrate form can lead to the selection of inappropriate excipients.

In many cases, the rate-limiting step in comparator development is the

development of analytical methods. Obviously without the appropriate methods, the development scientist has no means of evaluating the effect of blinding manipulations on stability, dissolution, and other product attributes. Although some relevant information is available through sources such as the Freedom of Information Act, an experienced methods development chemist is invaluable in expediting comparator development. With the analytical tools and preformulation results in hand, abbreviated formulation and process development studies are initiated. The formulation studies should include short-term stability, excipient effects, limited process characterization, comparative dissolution for solid dosage forms, and depending on the degree of manipulation, in vivo bioequivalence testing. To protect the integrity of future clinical supplies, it is critical that products produced for a bioequivalence test use the same formulation and process as any future supplies. Bioequivalance testing is typically costly in terms of time (2 to 6 months) and money ($50,000 to $150,000). Some ultraconservative companies may perform bioequivalence testing on all manipulated blinded comparators. Some companies only perform bioequivalence testing for substantial dosage form manipulations. Substantial manipulations would include tablet milling and recompression, encapsulation of broken unscored tablets, developed formulations from raw drug substance, and refilling of encapsulated powder. Additional in vivo versus in vitro testing information is located in the comparator testing section of this chapter.

E. Comparator Testing

Development of analytical methods and product specifications is an integral part of any new product development. The most commonly used analytical test for comparator products is ultraviolet (UV) or high-performance liquid chromatography (HPLC) based. The methods are developed around a drug substance standard that usually is available from the innovator or through the USP. In some cases, where the reference standard is unattainable, the innovator marketed product has been used as a "standard." In this case, the assumption is made that the marketed innovator product meets assay and dissolution specifications and that by demonstrating comparable adsorption or peaks, the developed blinded comparator also meets specifications. This is certainly less than ideal but may be the only avenue available. When a drug substance reference standard is available, precise validated methods can be developed for identity, dissolution, assay, and residual.

Perhaps the most involved area of testing blinded comparators is comparative dissolution profiles for solid dosage forms. For immediate release products, the dissolution rate of the blinded comparator and the innovator product is monitored in 5 to 15 minute intervals over 60 minutes. For delayed release dosage forms, the test intervals range from 1/2 to 3 hours over 8 to 24 hours.

The resulting dissolution rate profiles are then compared. This comparison may be evaluated by a development scientist, a pharmacokinetist, or the entire developmental project team. If bioequivalence is in doubt, either the blinded comparator is reformulated and retested or an in vivo bioequivalance test is performed.

The issue of bioequivalence is extraordinarily significant for two reasons. First, if the blinded comparator is not bioequivalent to the innovator product, there may be substantial medical risk to the patient. Second, the ultimate conclusions and impact of the clinical study are in doubt since the innovator product serves as the benchmark of efficacy, safety, and adverse reactions during the study.

Another important aspect of analytical testing for blinded dosage forms is stability testing. Since limited stability data is available, pharmaceutical companies typically do not assign expiration dates for their clinical supplies. Instead, real time data are used to support and justify the continued use of the materials in the clinic. Most companies assign a retest or stability review date for each product and essentially extend the review date in 3- to 12-month intervals as justified by the stability data. The stability samples should be packaged in the same container closure system as the clinical supplies in the field or be packaged in a worst case package. This ensures that the stability data will provide adequate support for the products in the clinic.

VII. DOCUMENTATION

A. Clinical Manufacturing Batch Records

Just as clinical supply manufacturing must comply with cGMPs, the resulting batch record documentation must also be completed in full compliance with cGMPs (8). This requires that the batch record include all process controls, product specifications, and accurately recorded relevant information, and that each critical step or process be witnessed by two individuals. With this background, a master clinical batch record must allow the scientist to remain in compliance with cGMPs while providing the needed flexibility to develop and manufacture clinical dosage forms in early clinical development (phase I–II). Unfortunately, the required information for setting tight in-process controls and product specifications is typically not available until the first few batches are produced. The challenge then is writing a clinical manufacturing batch record is to provide the controls required for compliance while maintaining enough flexibility to allow the scientist to both develop and manufacture the product concurrently.

This can be accomplished by incorporating broad acceptability ranges into the product specifications, in-process testing, and operating parameters of each

process step. As an example, rather than specifying "blend for 15 minutes," the clinical batch record could specify "blend for 10 to 20 minutes" followed by a recording of actual blend time. For complex, multiparameter processes such as film coating, the process parameters can be specified as target values followed by a recording of the actual run value for each parameter. This approach provides for a review and approval of specifications and process parameters during the master batch record approval, maximizes flexibility to the development scientist, and minimizes the number of "exception reports" (for operations that exceed set parameters or specifications) required for clinical supply batches.

The clinical manufacturing batch record typically becomes more detailed and less flexible as the later stages of clinical development are reached (phase III). It will include much of the processing and scale-up information obtained from the early developmental and clinical batches, and it is common for batch records at this phase of development to include the same process controls and product specifications as those intended for the NDA.

The contents of the clinical batch record often are specific for each product; however, a core set of "sections" should typically be included. Theses include an approval section for the master, a formulation section specifying the quantitative and qualitative composition, safety dispensing, processing instructions, in-process recordings, reconciliations(s) for each major process step, and final sign-off by the operations scientist and quality assurance.

B. Supporting Documentation

In addition to the completed manufacturing records, several other documents should be directly traceable to a clinical manufacturing batch. These include a completed checklist covering the review and approval of the batch records, a separate approved master batch record, equipment use logs, cleaning documentation, and investigation reports for any major problems incurred. Also other more general documents that are linked to the batch should be retrievable. These would include standard operating procedures (SOPs) for all phases of the operation (equipment, facility, operations, and support systems), calibration and maintenance records, inventory records for raw materials and finished products, laboratory records including raw data, analytical methods and specifications, stability data and reports, and validation records (protocols, reports, and raw data) including a complete validation package for all equipment, controllers, utilities, and facilities (9). Finally, for clinical supplies destined for use in the United States, a copy of the filed IND (NDA for phase IV studies) should be available. Having the quality control unit (Quality Assurance) review the final documentation package against the most current version of the IND is a critical step just before release. It is at this final step that the conformance of the

Introduction (brief overview)	Container Closure
Drug Substance	•Description
Drug Product	•Supplier
• Components	•Specifications and Methods
• Composition	•Drug Master File Reference Letters
• Batch Formula	Packaging Process and Controls
Specifications and Analytical Methods	Sampling Plan
Sites (Drug Substance and Drug Product)	Regulatory Specifications
• Manufacturing	Batch Release Data
• Packaging	Analytical Methods
• Testing	•Suitability
Typical Suppliers of Components	•Methods Validation
Methods of Manufacturing and Packaging	Stability of Drug Product
•Manufacturing Process and Controls (includes flow chart)	•Stability Protocol
•In Process Controls	•Stability Data
	•Storage Condition
•Reprocessing Operations	•Commitment to do Ongoing Studies
	•Supportive Data

FIG. 3. Typical contents of the CMC section of an IND.

formulation, process, controls, methods, and specifications are reconfirmed. Fig. 3 lists the typical contents of the chemistry, manufacturing, controls (CMC) section of an IND. The contents and degree of detail required in the CMC section is dependent on the type of product under development. For an NCE or an entirely new dosage form, the IND should be comprehensive and fairly detailed. Amendments for comparators or slight formula and process changes typically are quite brief in scope and content.

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9

Clinical Supply Packaging

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I. INTRODUCTION

A. Overview

The operations of a clinical supplies packaging area are similar to other pharmaceutical packaging functions. However, it is the uniqueness of its processes that sets it apart. To do justice to this subject, it is necessary to show the critical interfaces that occur with other related functions under the broad heading of Clinical Trials.

B. Function

Specifically, the function of a clinical supply packaging group is to fulfill the following:

1. Transfer manufactured dosage form* (1) into drug product for use in a clinical trial, while operating in a "zero defect" environment.
2. Provide documentation ensuring adherence to current Good Manufacturing Practice (cGMP) requirements and Food and Drug Administration (FDA) regulations.
3. Ensure that label text and the design of supplied drug product meet the criteria stated in the protocol.

*The nomenclature of the September 22, 1994 ICH Guidelines is used here, distinguishing between drug substance (bulk drug), dosage form or preparation (e.g., tablet, capsule or liquid), and drug product (packaged dosage form).

4. Interact with other branches of the Clinical Trials Function to facilitate, optimize, and expedite the performance of the function as a whole.

C. Operating Philosophies

As mentioned, the function of the clinical supply packaging group of an organization is to convert bulk drug dosage forms into the packaged unit. This function differs significantly from the packaging function for manufactured, marketed product in several aspects:

1. The dosage form (tablet, capsule, liquid, or topical) is of a developmental character and does not have the "previous batch experience" associated with a marketed product.
2. The drug product is earmarked for a clinical, investigational setting, and not for routine hospital or consumer use. For this reason there is:
   a. An instructional or educational component to the product (i.e., the health professional and investigational personnel have not previously encountered, or to a limited extent encountered, the properties or actions of the product).
   b. A blinded component, in the sense that the product is blinded to the site personnel (double-blind study) or only to the patient (single-blind study).
   c. The use of specialized containers and packaging techniques to foster patient and site compliance.
3. The stability and compatibility of dosage form and packaging component are not as completely known in the clinical setting as they are for marketed product, where they are *well* established by data from long-term stability studies. However, preliminary data must exist supporting the expectation of stability. This must be confirmed by concurrent stability studies.
4. The batches are most often of a smaller scale and involve small scale packaging (which in itself can be challenging) as opposed to routinized, automatic packaging as encountered for the marketed product (2). This, as a result, requires "small-scale" packaging equipment. A good example is the utility of a small form/fill/seal machine, which has short set-up and change-over times, affordable tooling costs, and operates with easily learned skills by a minimum of personnel. There is no need to have all the "bells and whistles" associated with a production blister machine where the dosage form is placed into the hopper at the start of the blister line and a blister card placed into a packer as the end result. For clinical trial materials, this sophisticated type of equipment can actually be cumbersome and inefficient. The clinical supply pack-

ager needs equipment that is small (space considerations), flexible in use, yet easy to maintain and operate with a minimum of personnel.

5. Specialized techniques (e.g., separation of process steps, use of physical barriers, utilization of colored templates as a visual aid) must be implemented for dealing with blinded materials during the secondary packaging (placement/sealing of the blister strips into the card-stock) and/or the assemblage operation. Phase III trials often require the use of blinded (different drug products that are identical in appearance), active, placebo, and/or positive control drugs. In this way, a bias response by the investigator or the patient is eliminated.

Stringent control must be exercised to ensure the correct placement and labeling of these materials. Stringent controls in this context would include double-checking procedures, attention to documentation, and meticulous in-process labeling.

II. COMMUNICATION, SCHEDULING, AND PLANNING

A. Communication

As in other aspects of industrial achievements, communication is the key to success. In clinical packaging, communication is probably more of a necessity than in any other part of the developmental chain of information. In terms of cost, Moran (3) indicated that the cost of information accounts for 65% of the variability in the price (based on the number of case report forms) of the clinical trials, thus emphasizing the import of communication even on a financial basis.

The chain of information leading to clinical packaging starts with the proposed Investigational New Drug (IND) application, containing the planned well-controlled studies showing safety and efficacy. More often than not, no matter what obstacles and/or time delays are encountered during the developmental stages, the shipping of the clinical supplies is usually planned for 30 days after filing of the IND. Definitive, quality planning is critical, but often lacking.

Conceptualization (4–6) of the transformation of scientific findings pre-IND into a clinical program post-IND requires all of the functions described in this and other chapters of this book. It is obvious that intercommunication is important for the sake of efficiency, as well as for general adherence to regulations. What is here emphasized is that a clinical master plan (CMP) is necessary.

The CMP, which describes the planned studies, addresses such questions as the following: What is the anticipated action of the drug substance? Particularly, how many patients, or protocols would be needed to statistically demonstrate that a certain clinical effect is obtained? This is of course, the reason that

placebos* are included, because they establish the base line (7–9). This plan would also allow for the manufacture and packaging of the necessary materials as one "batch," if all proposed studies were included. The support groups (analysis, compliance, etc.) could then perform the necessary activities one time, rather than repeatedly. This can be time-saving and allows for resources and equipment to be allocated to other projects. Expediency in clinical trials is a byword.

A protocol, therefore, must be established by the clinical and/or medical department in conjunction with the statistical area. This latter contributor is important in the achievement of the clinical goals just mentioned. It is necessary to calculate beforehand, the size of the patient population necessary to prove a definitive effect.

Although the CMP has been presented as if it were completely in place by the time the product reaches the packaging phase, this is by no means true. Protocols constructed without the expert input from the associated branches, such as clinical packaging, usually have to be revised. Often, the actual packaging designs (bottles versus blister cards) are arrived at by discussion between the clinical/medical and clinical packaging areas.

When the protocol has been finalized (or at least in a "final draft" stage), the clinical packaging area becomes mobilized. The decision is reached as to whether to package "in-house" or use contract packaging companies. This decision is based on the availability of internal resources and time constraints.

The packaging action plan (PAP) is written for each protocol. The PAP for a protocol can be likened to a building block, with several PAPs comprising the CMP:

$$\sum_{n=1}^{\infty} PAP_n = CMP$$

This details the critical information needed to completely prepare the clinical materials for shipping (Fig. 1).

Such a plan establishes communication, sets the desired results, and is useful for both contract and in-house packaging operations. It can be as detailed (listing study objectives, inclusion/exclusion criteria, etc.) as desired.

After completion of the PAP, and before its implementation, job work orders (e.g., for primary blistering, carding, labeling operations) should be issued to initiate the process. A computerized template for the job work order form helps to facilitate this step. The use of such forms actually aids in the

*In Japan, it is difficult to obtain consent for placebo-containing studies; some hospitals consider the use of a comparator placebo as unethical and will refuse such studies.

PACKAGING ACTION PLAN FOR PROTOCOL XYZ

Protocol XYZ (Unit Dose Study)
Title:
Drug Products:
Lot Numbers of Drug Products:
Amount of Drug Product Needed:
Card Design: Details the design (i.e. treatment legs, crossover design, subjects/treatment, etc.)
Number of Patients: **Evaluable** _____ **To be supplied** _____
Duration of Study:
Card Components: Description of card-stock, heat seal material, etc.
Number of Cards to be Prepared:
(#)cards/leg needed for study + (#)cards/leg for testing + (#) cards/leg for retains = Total (#) cards/leg

TOTAL CARDS NEEDED = (#)Cards [(#)cards/treatment leg x (#)treatment legs]
Dosage Form Size:
Packaging Components: **Film:** (Manufacturer, Lot # etc.)
Lid-stock: (Manufacturer, Lot # etc.)
Labels: Positioning of labels (auxiliary, spine, double-blind, etc.).
Number of Sites:
Block Size =
Packers: Number of cards/packer; packer has packer labels positioned on front and top of packer.
TOTAL NUMBER OF PACKERS =
Randomization: Numbers will run from ___ to ___.
Shippers: (#) packers (each packer holding (#) cards) placed into an over-packer.
Place (#) packer(s) into shipper. Indicate Patient Range on each shipper.
Total number of Shippers =
Stability Requirements: (#) "nicked" sheets, consisting of (#) units/sheet.

FIG. 1. Packaging action plan (PAP).

planning and forecasting of clinical packaging events. For example, if there are several job work orders on file calling for bottling runs of varying sizes, the run that best fits a time slot can be selected.

B. Scheduling and Planning

In scheduling and planning, the time required to complete a clinical order is of utmost importance. It should never be forgotten, however, that the most important facet is the quality of the finished product. Quality must be built into the process; it can never be added later.

The scheduling and planning for packaging are affected by two major factors, the priority of the study and the requirements of the protocol. *If the design of a protocol is ever altered* to include more or different dosage units or

components, it stands to reason that, in most cases, the original schedule will not be met. Any change, no matter how trivial it may appear to others, will have an impact on the original timing—sometimes slightly, more times dramatically. In the real world, this realization rarely materializes.

C. Realistic Time Line

In planning for clinical studies (as well as for other phases in the development of a product), there is usually a chain of critical events. Essentially, at the onset of the development of a product, reasonable dates at which a given phase of the development can be expected to be completed (critical paths) are forecasted and subsequently monitored as to progress.

For example, if it is anticipated that the IND will be filed in December of the current year, phase I studies could hypothetically be started in January of the next year. From a "time-accounting" point of view, 30 days after filing the IND, with FDA agreement, or if the FDA has not responded within this legal period, the first clinical supply materials can be shipped. From a clinical point of view, clinical investigators would have to be enrolled; from a clinical manufacturing view, raw materials would have to be available; from a clinical packaging point of view, packaging components would have to on hand.

One factor is often overlooked. Most companies have more than one project in development, and therein lies the problem: Are equipment and personnel available? If for instance, the clinical department states that "they want something by a certain date," then it must be realized that this may not be possible. If the bulk dosage form cannot be produced by that date, then the batch obviously cannot be packaged. Or if on-track priority products have the packaging department fully scheduled, either the new request must be declined as unrealistic, or something else must be delayed.

In some instances, a study demands that a "critical ship date" be met. If the information needed to support an indication relies on enrolling subjects with certain symptoms or illness (e.g., fever, allergy, cold/cough), then the study must be fielded during the appropriate season ("window of opportunity") or the compilation of data could be delayed for a year. Obviously, realistic preplanning is especially important for projects of this nature.

To delay operations, it is not enough to simply reprioritize. If the packaging for a study is underway, it is inefficient and may compromise quality if one stops in the middle of a large filling run. It is unrealistic to expect a packaging group to cease operations and immediately begin a different project. Equipment needs to be cleaned, and documentation needs to be completed indicating the shut-down; these are cGMP requirements. Realigning priorities should affect future studies first and foremost, rather than those currently being worked on. Using this approach results in greater efficiency.

III. CHOICE OF PACKAGE

A. General Considerations

The package selected is influenced by (a) the type of study, (b) the stability of the product, (c) the size of the order, and (d) frequency and duration of the dosing regimen.

The first consideration is, of course, what type of regimen and control are needed and often centers on whether packages (e.g., bottles, pouches) or blisters should be used. Patient and site compliance and ease of use for the patient are important factors.

The second aspect depends on the extent to which the product is light, moisture, and oxygen-resistant. In some cases, the stability of the product dictates the package.

Next, the package can be a function of the size of the study. For a small preliminary study, it might, at times, be preferable to simply manually package into bottles in lieu of unit dose systems.

Finally, the expediency of the trial may also dictate a container choice in that a study can be fielded more quickly packaged in a bottle than in a blister card.

In general, however, the package should be inert to the product within, be tailored to the study, allow for the easiest and most accurate accumulation of clinical data, and offer the greatest assurance of patient and site compliance.

Before the mid-1970s, most clinical packaging was carried out in amber glass bottles, which were screw-capped in a fashion as close to hermetic as possible. This would allow assurance of integrity of the product at the time of clinical use, and as such served a philosophy of assurance at the "time of delivery." By such a philosophy, the stability of the product would be carried out in the hermetic container. Once it was established that the product was market worthy, packaging trials would be initiated to select suitable market packages.

Using this sequential scheme, time is lost at "the end", since stability studies must be carried out in the proposed marketed container. The intent of clinical trials is not dovetailed to stability assessment in final marketed containers, but valuable information can be gathered during clinical trials that will aid in the selection of the final package.

If the product is for over-the-counter (OTC) use, or is being considered as a candidate for a switch from a prescription product to OTC status, a proactive company would include marketing in the planning stages. If marketing has an early input as to the final marketed design, an early assessment of product stability in the final marketed container can be achieved.

B. Stability Considerations

The first piece of information that is necessary in the selection of a package suitable for a clinical trial is whether the product is:

1. Very stable (solid and liquid dosage forms)
2. Sensitive to moisture* (solid dosage forms)
3. Light sensitive (solid and liquid dosage forms)

There are (as required by the guidelines for submission of the IND) already preliminary tests that will answer the preceding questions. When a product is "rock-solid," great leeway exists in the selection of packaging components.

If a product is very sensitive to moisture, then desiccants may have to be added to the container, or suitable film selected that will afford moisture protection. If a product is light sensitive, then some sort of light protection is required (e.g., amber film, opaque blisters, opaque hard gelatin capsule shells). Furthermore, a blister may not be possible.

The needs of the product must be defined, and the packaging must reflect these needs. In essence, the needs of the product should be determined, then it should be packaged to meet these needs. Do not package first and discover later that the package failed to protect the product. Component selection should be based on data, not on expediency.

The efficacy of the drug is of importance to the company. If it degrades too rapidly, or if pertinent parameters such as the dissolution profile shift during the study, the results of the clinical trial may be in jeopardy.

C. Effect of the Harmonization Guidelines

In the past, the distribution chain of a product in commerce was poorly controlled and not well regulated. This meant that the product could encounter high temperatures and relative humidities, and the "stability" profile ascertained in the constant temperature and relative humidity storage conditions in companies might not reflect the stability that the drug product would experience in the sales-train. Some companies address this issue with a transportation test, whereby the product is shipped to selected sites and returned for assessment. This test, however, is not reproducible because of variability (e.g., handling, routes taken, road status) and other unknown conditions to which the package is subjected. Also, seasonal variance necessitates repeated testing covering the four seasons.

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*As pointed out in the 1987 FDA Stability Guidelines, stable liquid products can at times cause "stability problems" because *loss* of moisture from the package can make the drug product superpotent.

Through the use of environment data recorders, the temperature, humidity, shock, and vibration that a product may experience during the transportation can be recorded. Once the transportation environment has been assessed, the data can be assembled into a test protocol for that product's specific transportation cycle. This protocol allows the user to design and test packaging in a laboratory environment with the use of temperature, humidity cabinets, and shock and vibration tables.

This test is reproducible and is conducted under known conditions (i.e., transportation environments). If the results demonstrate the package is not protecting the product, changes can be made to increase protection. Such proactive testing is cost effective, ensures products integrity, and hence increases customer satisfaction (10).

In the past, the FDA has attempted to counter the adverse effects in shipment by requiring that constant temperature testing of drug substances be carried out at 30°C (the average temperature in the United States is 25°C).

The Prescription Drug Distribution Act (11), requires that any storage area in which a drug product is stored be between 15°C and 25°C (not 30°C)* with the possibility of only occasional excursions to 30°C. It also specifies relative humidity (RH) conditions to be less than 60% RH. This means that the abusive temperature and relative humidity considerations alluded to here should no longer exist. Although compliance of the law may be some time in coming, its effect on the decision of how to package on the basis of moisture sensitivity will be affected.

Chapter 11 explains that the more units in a container, the less it will be affected by moisture permeation. In this respect, the blister is the most vulnerable package. This presumes a product is adversely affected by moisture, which is most often the case. Control of storage conditions in the market place will minimize the adverse affects, and in the future, more possibilities exist for packaging moisture-sensitive products in blisters, since moisture permeation will be less due to the more advantageous storage conditions.

D. Philosophy: Bottle Versus Blister Packaging

The quickest route to a packaged product is to use bottles, with the total quantity needed dictating whether to select manual, semiautomatic, or automatic bottling operations. In the case of complicated dosing regimens, however, patient compliance may be compromised.

It is difficult enough to ensure that the patient takes the dose at the correct times each day; but if also asked to take one tablet from Bottle A, three

*This does not apply to products which need refrigerated conditions (e.g., some protein products) in which case a refrigerated statement is included.

from Bottle B, and two from Bottle C in the morning and two from Bottle A, one from Bottles B and C in the evening, incorrect dosing is likely to occur.

The same request can be nicely handled by the use of medication blister cards, where the correct dosage taken at the proper time is indicted by directions for use printed on the card. Of course, this assumes the patient remembers to take the medication. The card does provide the patient visual evidence of medication taken, thus reducing dosing error.

With a new investigational drug, some physiological manifestations have already been observed in an animal species, and the first question is how that translates into effect in a human. Several questions must be answered, for example: What should the dose be? This is usually answered in phases I and II. This might seem to be simply a medical concern, but from the point of packaging technology, it is also a question of packaging.

In general, if one does not know a priori what the dose ought to be, one would first bracket the dose at various levels below what one would consider a maximum in terms of toxicity. Preliminary toxicity assessment has already been accomplished in the pre-IND stage, and the question then is the translation of effective and maximum doses from animal species to humans.

Although some scientific rules of thumb for species translation do exist, establishment of the effective dose and nontoxic doses is still somewhat empirical, so that the first clinical batches always bracket several dosage levels.

If these levels were, for instance, 5, 10, 25, and 50 mg, then one would obviously start with the lowest dose (since there is less chance of toxicity at this level), and then gradually increase it. Hence, it would seem that there would be a necessity for making four batches of product, each with a placebo. For a solid dosage form, this would entail the manufacture of at least five and maybe eight batches of product.

By the use of medication cards, it is possible to handle this situation by simply making three batches (placebo, 5, and 10 mg in the preceding case). For example, the 25 mg dose could consist of one 5 mg, two 10 mg, and two placebos in a row on the card (to satisfy the integrity of the blind, the two placebos are needed to satisfy the 50 mg dose, which would consist of five 10 mg units).

In this manner, packaging becomes an integral part of formulation of the dosage unit for the clinical trial. In addition, it will aid in clinical compliance and, therefore, in the assessment and submission of clinical data to the FDA.

It is exceedingly important to calculate, ahead of time (a function of the clinical department in conjunction with statisticians), the appropriate size of the study. Once the packaging is on track, it is very difficult and certainly very time-inefficient and expensive to make changes.

UNIT DOSE CARD OR PACKAGING NEED	Strength(mg)Test Drug 6.25	50	Placebo	Control(mg) 240	Placebo
Placebo (Baseline)					
Placebo (Treatment)					
6.25 mg Card					
12.5 mg Card					
25 mg Card					
50 mg Card					
100 mg Card					
150 mg Card					
Comparator Card					
TOTAL for Cards					
Stability Retains (Initial)					
QA Card Retains (10 Cards/Leg)					
Show & Tell Cards (10 Placebo)					
Blister Integrity Testing					
TOTAL for Packaging Processes					
TOTAL for Cards and Pkg Processes					
Packaging Overage (30%)					
Calculated TOTAL Needed					
CALCULATED MINIMUM AMOUNT NEEDED (TABLETS)					

FIG. 2. Example of calculation worksheet.

E. Calculation of Dosage Units Required

Although this subject would, perhaps, more naturally fall under Scheduling and Planning, its inclusion here is more appropriate, since it deals with the original blueprint of a clinical trial.

For involved calculations, which usually seem to need revision, a computerized spreadsheet should be used (e.g., Lotus). Any changes made in the basic parameters are thus automatically recalculated (Fig. 2).

Bernstein (4) uses the term *clinical protocol conceptualization*, which will be used here. It is important that, in the conceptualization process, the size of the study corresponds to the availability of drug product. If the total number of units needed is 20,000 based on the dosing of evaluable patients and that amount exists in inventory, one could assume that adequate supplies exist for the actual study. This would be inaccurate, however, since several other requirements must be met for regulatory and scientific reasons. These include the following:

1. Start-up losses during setup of equipment
2. In-process testing during the packaging operations
3. Yield lost during the run

4. Stability samples
5. Samples for release testing
6. Retains
7. Evaluable patient supplies versus actual patient supplies needed (to account for "dropouts")

Many of the preceding amounts will be ascertained by experience with the equipment and from requirements set in internal standard operating procedures (SOPs). A retention guide in sliderule format is available to members of the International Society for Pharmaceutical Engineering (ISPE). The guide indicates the required quantity of retains, the retention period, the FDA reference, and recommendations (12). Peer knowledge gleaned from professional societies, such as regional clinical discussion groups, are invaluable and should be considered a prime source of information.

F. Schematic Representation of Packaging Plans

The need for communication has been greatly stressed as the key to successfully accomplishing the task of fielding clinical supplies in a timely manner. If the communication is accompanied by pictorial representations (e.g., the medication card, the packer assemblage), then the "surprises" are few. The use of a computer assisted design (CAD) software program to draw accurate schematics can be helpful not only in discussions with the medical staff concerning the correct interpretation of the protocol, but also when negotiating with contract packagers or as a guide to the packaging personnel.

Such a schematic is shown in Fig. 3. Assume the protocol called for dosing to begin at 2:00 PM on the first day in order to perform a laboratory test before medication. Doses on days 2 to 6 were to be taken as indicated. If all cards are identical, then there might be patient confusion on the first day, resulting in delay or loss of an evaluable patient.

The presentation of the schematic not only is useful in allaying the physician's fears, but also conceptualizes one's needs for the contract packager and helps the analytical staff plan the strategy for ensuring correct placement of the dosage units during the final identification testing.

This design, calling for two different medication cards, would need two separate cutting and printing jobs, resulting in added expense. Another schematic (Fig. 4) shows how the same card can be used (one printing and cutting job) and still achieve the same compliance. All cards in this second schematic have the covers of the blister openings perforated with "Unfilled" printed on the top. For day 1, this perforation is not removed; for days 2 to 6, this cover is removed and filled with a blister. It is good policy never to have "intentional" empty blisters on a medication card. Experience demonstrates that the patient,

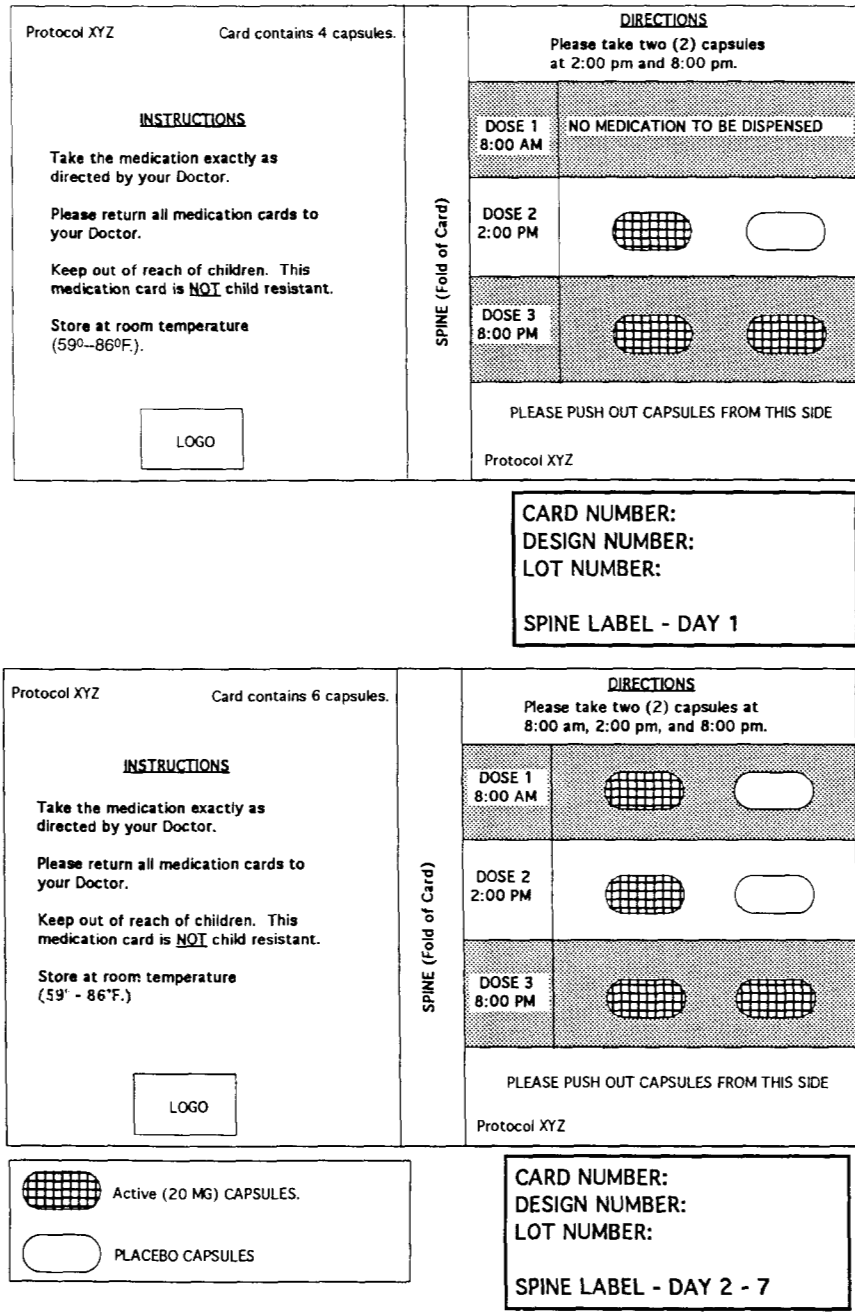

FIG. 3. CAD schematic of a medication.

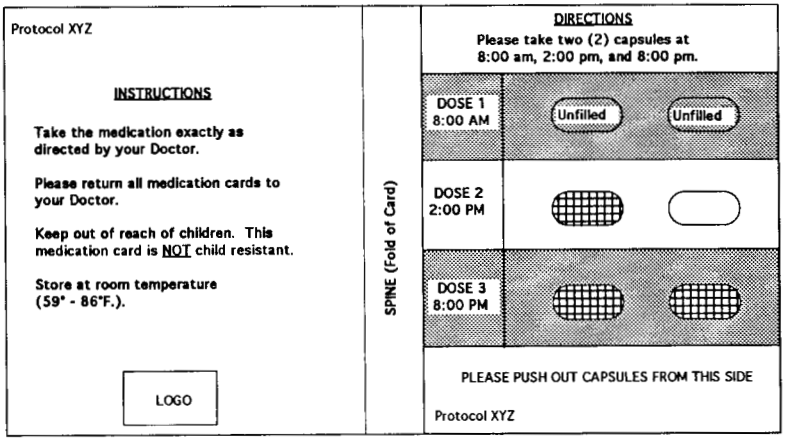

FIG. 4. Generic design.

when confronted by an empty blister cavity in a medication card, believes a mistake has occurred. Consequently, compliance suffers due to uncertainty.

These schematics are also able to depict the treatment legs by using differing shading or cross-hatching designs to represent each drug product or different strengths of the same drug product. This study has four treatments, each with a different placement of the active dosage form. Drawing these in full detail ensures that the protocol has been interpreted correctly and that those involved are in agreement as to design. If label placement is critical, indicator placement marks must be printed on the card.

The CAD system is also useful for tooling design, for cutting die designs needed for heat sealing nests (the board on which the blisters are sealed to the card-stock), and as a visual aid to the packaging staff in complicated assemblage operations (see ASSEMBLAGE).

IV. PACKAGING COMPONENTS

A. Overview of the Selection Process

The clinical packaging area will have little decision in the choice of components used, other than whether to use a bottle, pouch, vial, or a blister type of container. Even that decision is dictated by the requirements of the protocol.

Corporate philosophy, plant (operations) preferences, cost benefits negotiated by purchasing, and availability all have a major impact on the selection. However, the stability profile of the drug product is the most important factor for a packaging area to consider when choosing a component.

Often, operations may not wish to run a certain type of film because of tooling wear; purchasing wants only polyvinyl chloride (PVC) used for cost containment; marketing wants a certain shape/size bottle. At the proper time,

these views should be considered. In phase I and beginning phase II studies, most drug products are in the early stage of their development and long-term data have not yet been accumulated. Hence, a conservative approach by the packaging area is most warranted. Initially, this means the use of the most protective components available, regardless of cost. Valuable time, money, and loss of data can result if the product degrades during the duration of the study.

Choosing flexible packaging materials (films) can be a puzzling task. As a rule, initial stability protocols do not include blister units. As mentioned, the blister unit is the most vulnerable package. For this reason, most clinical packaging areas rely on either polyvinylidene chloride (PVDC) or trichlorofluoroethylene (Aclar*) film for early unit dose studies. If the decision is later made to market the product in blisters, the packaging area can assist by preparing samples for stability using the various films.

Choice of bottles should be the same as those used by operations. This is recommended not only for cost containment, but also to ensure a ready, ample supply and reduce storage space needed for inventory. Wadding (cotton or rayon) should be similarly handled.

The bottle closure (cap) may be a different matter. The majority of clinical packaging areas are using induction sealing equipment for obtaining a tight liner fit and have abandoned the "glue-pot" method. In some cases, this method has not been implemented by operations for marketed products, necessitating inventory of the desired caps.

B. Child-Resistant Packaging (CRP)

It is strongly recommended that regulatory be consulted when setting internal guidelines for the use of child-resistant packaging (CRP) for investigational materials. The FDA has not specifically stated that CRP be used for clinical supplies. The United States Poison Prevention-Packaging Act of 1970, enforced by the Consumer Product Safety Commission (CPSC), publishes a list of substances that require CRP. Prescription drugs and controlled substances are included. It is apparent that when a marketed prescription drug is used as a blinded control, CPR must be used or the package can be considered "misbranded" and in violation of the Act. The recommendation to use the components from the operations area has even greater import in that these components will satisfy the requirements.

In the case of blister cards, the solution for a clinical packaging area is not easily found. One design that has met the CRP requirements involves a card with perforated blisters, backed by material resisting "push-through" access. Normally, aluminum foil is used for "push-through" ease of opening. The

*Aclar is a registered trademark of Allied-Signal Co.

blister contains a slit perpendicular from the perforation to the blister compartment, which is torn by the consumer to remove the drug product. This design is widely used by pharmaceutical companies. CPR requirements are met based on the assumption that a child cannot readily perform two sequential opening motions. However, the cost of tooling for the slit design is higher, and new tooling would be required for changes in configuration. It is not practical to use the design in a clinical setting and, if required, would probably eliminate the use of the medication card for clinical studies. As mentioned, the use of medication cards is perceived to improve patient and site compliance.

The clinical packager is then faced with two diametrically opposed issues: package following CRP requirements or following the FDA guidelines for well-controlled studies. Presently, most clinical packaging groups are printing a statement on the card denoting that "This medication card is NOT child-resistant" (Fig. 3). The statement is usually highlighted by use of color (red) or other graphics (boxed).

CRP is not considered to be elder-friendly. To resolve this issue, the CPSC has instituted a major change for testing standards (13). The revision stipulates that testing for adult effectiveness will include subjects 50 to 70 years of age. The age range had been 18 to 45. It is the senior adult who most needs medication.

The senior adult use effectiveness (SAUE) requirements together with the need for child-resistant (CR) closures may result in package changes is closures do not meet the CPSC testing standards. Pharmaceutical packagers must be able to prove to the CPSC that their packages are CR and elder-friendly (14).

For clinical studies concerned with arthritic conditions, it would be reasonable to have an easy-to-open package. The consequence of a difficult-to-open package could result in noncompliance. For example, a patient could decide that the package requires scissors to remove the medication and then decides to save time by cutting open all the blisters at one time and placing the medication in an easy-to-open container. The carefully controlled, identified-by-assay, blinded configuration of one active plus 2 placebo units taken four times each day is destroyed. The patient could take a dose consisting of three active units and perhaps suffer an adverse drug reaction (ADR).

C. Tamper-Evident Packaging

Tamper-evident packaging is not required for clinical supplies. However, there is a shift toward this safeguard by most pharmaceutical companies. Furthermore, there is a psychological expectation by the consumer to find this packaging on products intended for human ingestion (e.g., food, beverages, health products). To do less might create a negative impression. In addition, tamper-evident sealed packages can expedite accountability of returned goods. If the

seal is intact on the returned package, there is no need to count the enclosed product.

The most commonly used tamper-evident protection is the shrink-band. This usually consists of a PVC sheath placed over the neck of the bottle and then run through a heat tunnel to shrink the band to the bottle conformation. Attempts to carefully remove or expand this band by water, heat, or solvents will fail.

The use of tamper-evident tape on patient packers is common. The tape can be made tamper evident by either having it contain cuts or removable printing. Tape can be purchased containing a series of designed cuts, which after application to the packer are impossible to remove and reassemble to the original condition. Print-removable tape ensures that once the tape has been lifted or removed, the color remains on the packer, making reassembly difficult. Tamper-evident tape imprinted with the company logo presents an elegant, professional package to the investigator. It also indicates a concern for the integrity of the study supplies.

D. Containers and Closures for Bottled Supplies

The submission to the FDA of an IND or New Drug Application (NDA) must include detailed information concerning the packaging components. This is included in the Chemistry, Manufacturing and Controls Section (CMC). Any component in direct contact with the drug product (primary container) must not interact, physically or chemically, or alter the strength, quality, or purity of the enclosed product.

In addition to quality assurance (QA) testing performed by the company for release, FDA and cGMP regulations also require component testing. The latter testing is usually more detailed and is performed by the component manufacturer. The resin used (bottles) or the composition of a laminated film must be stated. In cases where this information is considered proprietary by the component manufacturer, information in the Drug Master File (DMF) can be utilized by the FDA. The DMF is submitted to the FDA by the manufacturer of the component.

The most commonly used multiple use container is the high-density polyethylene (HDPE) bottle. The United States Pharmacopeia (USP) may be referenced for definitions, descriptions, and examples. Bernstein and Tiano (15) presented an overview of some of the more commonly used containers.

The USP defines/describes the following: light-resistant container, well-closed container, tight container, hermetic container, single-unit container, single-dose container, unit-dose container, multiple-unit container, multiple-dose container, and containers for articles intended for ophthalmic use. Containers are available that offer protection for light-sensitive, hygroscopic products. The

cost is similar to that of a white HDPE bottle while providing the light resistance and moisture protection of an amber glass bottle (16).

As mentioned, in addition to utilizing supplies from operations, it is also recommended that the packaging area restrict the number of choices to their customers. By offering two or three bottles of differing capacity, the packaging area can decrease the workload for the stability area and decrease storage requirements. If no restriction is imposed, the support groups will be overwhelmed.

E. Films and Foils for Blister Use

It is best to err on the side of conservatism when selecting a film for blister use. The use of PVDC or Aclar is recommended until the stability profile supports film of lesser barrier properties. The best source of information concerning selection of the film for a drug product is the component supplier. If one knows the sensitivity of the drug product, the supplier can suggest films offering suitable barrier protection. PVDC (40 to 60 g/m^2) is laminated, usually to PVC (bilaminate), and offers varying degrees of barrier protection, based on the thickness of the PVDC coating. If a film is described as a trilaminate, the third layer is usually polyethylene sandwiched between the PVC and PVDC (40 to 150 g/m^2) layers.

The "green movement" has prompted manufacturers to develop new films that address environmental concerns (release of vinyl chloride into the atmosphere). In Japan, oriented polypropylene (OPP) has replaced PVC as blister material. Processing difficulties are associated with the forming and sealing of OPP, especially when using older equipment. If necessary, OPP capability can be achieved by updating the equipment.

Aluminum foil is the usual choice of backing or lid stock for the blister unit. According to the process used, foil is described as either "hard" or "soft." Hard foil, used commonly in Europe (17), is more brittle and "cracks" open easily, thus preventing the possibility of aluminum debris. Soft foil (the annealing process softens the hard foil) tends to have fewer pinholes than hard foil. One must be careful to specify which foil is used in the CMC. It is proactive to conduct stability studies proving interchangeability for products, if both are to be used in the packaging area.

The use of perforated tab backs over the foil lid stock is a common practice. This technique protects the foil from inadvertent puncture but is not deemed user-friendly by the patient. Since punctures are most likely to occur during the manufacture of the sharp-cornered blister strips, one should be prepared to conduct a 100% inspection of the prepared strips. Round cornered strips can be manufactured, but tooling cost outweighs the advantages for the clinical packager.

V. PACKAGING EQUIPMENT CONSIDERATIONS

When considering equipment, there is a tendency to think in terms of full production lines, and hence adopt a large scale packaging approach. This is inaccurate. However, for very large trials, such as phase IV, it is recommended that operations be consulted for unlabeled packaged product. Also, it would be foolhardy to set up a high speed line to package 500 bottles. One must think in terms of "small-scale." For small packaging runs, bottles are often manually filled.

The following discussion on packaging equipment begins with a section on Validation, a necessary process for all packaging areas. A good presentation on this subject is given by Jenkins and Osborn (18). If new equipment is being purchased, valuable information concerning the critical parameters can be obtained from the vendors, thereby facilitating the procedure.

A. Validation

The FDA defines validation as "establishing documented evidence which provides a high degree of assurance that a specific process will produce a product meeting its predetermined specifications and quality attributes" (19). In essence, what is being asked of the industry is that it document that it is able to produce a quality product using a particular piece of equipment.

The first step is to write the validation protocol, which is a thoughtful outline of planned tests thus ensuring that the equipment is performing as intended. Basically, the installation qualification (IQ), the operating qualification (OQ), and if possible, the process qualification (PQ) are itemized. PQ is difficult to accomplish in a clinical supply area because of the varied packaging processes. Rarely is a process repeated.

It is suggested that the protocol contain specifically designed forms or areas for entering the individual test results. This approach is time-saving. The protocol is then submitted for review and approval by the compliance department. (Depending on the company, this function may be performed by QA, Regulatory, or other department.) After approval, documented testing begins.

The key phrases are "thoughtful outline" and "documented testing". A good example for "thoughtful outline" is given by Larson (20). If one is validating the bottling line, the critical areas would be the filling station, the cottoner, the capping/sealing station, and labeling. Why worry about whether the accumulation table works satisfactorily? The bottles will accumulate, and if the cartoner, afterwards, does not function as well as desired, the final outcome is still a quality drug product. The phrase "documented testing" simply means recording observations. If there are no records, the FDA will assume that the validation has never been performed. In the clinical setting, it is im-

portant not to overapply the concept of validation, but rather to analyze and think, and then ask the question: What is important for the quality of the product?

IQ involves the testing needed to prove that the machine meets the specifications and performs the operations for which it was purchased (e.g., On/Off switch is operational). It is necessary to determine the operating limits and challenge them (usually the manual will indicate the operating range). After familiarization with the machinations, it is wise to write the SOP indicating the correct procedures to be followed for operating the equipment within these limits.

OQ follows and involves the testing and challenging phases to demonstrate the effectiveness and reproducibility of the operation, including the "worst-case" scenario (e.g., for a filling station, the use of odd-shaped tablets).

Revalidation must be considered when there are significant changes in packaging components or changes to the equipment. If one decides that, for a blister machine, future films used will be limited to three types (PVC, PVDC, and Aclar), one should proactively include these in the original protocol.

B. Container Filling and Counting of Solid Dosage Forms

The filling may be accomplished manually, semiautomatically, or automatically. The degree of sophistication attained is usually cost and time based (21). The most important condition to be met for all variations is that the fill be accurate and satisfy requirements (accountability, QA/compliance, regulatory). One hundred percent accuracy must be achieved at all times ("zero-defect"). However, one cannot ensure this criterion except by recounting every container. In large studies, the time factor needed to supply the study materials under such conditions would be unacceptable. The confidence limits for the equipment have been established during the validation of the equipment. Strict adherence to preventive maintenance procedures, in-depth training of personnel as to set-up and operating procedures, well-written SOPs, in-process testing, and documented reconciliation are measures that will help attain the 100% accuracy demanded.

C. Manual Filling of Solid Dosage Forms

Manual filling (counting/filling by hand, with a 100% second count) is the most accurate, albeit the most time-consuming, labor-intensive method available. In the interest of time, this method is usually reserved for the smaller (less than 500 containers) studies containing 1 to 100 dosage units per container. Manual filling is very operator dependent, and even the most conscientious operator will suffer fatigue. A random check of the filled containers is not sufficient.

One method used to reduce the time factor and eliminate a total recount is to perform a weight check on each container. This technique is acceptable providing that the balance can detect a one dosage unit discrepancy (if that is the specification stated in the SOP). It would also be wise to determine the weight variability for that particular lot of containers. Each lot of containers should have a minimal variation; however, if the lot is changed, this variability must be checked. The new lot could have been manufactured using a different mold. Due to the increase in packaging demands and time restraints, most packaging areas have assessed the "cost-value" attained and instituted some form of automated filling.

D. Bottling Lines for Solid Dosage Forms

A typical bottle filling line will use either an electronic or slat/disc container. With an electronic counter, the product falls into a container after breaking an (or series of) electronic beam(s). In a slat/disc, the product falls into a precut grid, is checked, and then is allowed to fall into the container.

Equipment can be as simple or as high-tech as desired. A counting unit that counts each dosage form as it passes into a funnel positioned over a bottle that is held and switched by an operator would require a minimum of training or mechanical knowledge to produce the desired result. However, an automated line whereby the dosage forms are placed into a hopper, the desired setting entered, and the bottles continuously filled, checked, wadding added, checked, capped, sealed, checked, and retorqued, as they move along the conveyor belt to the final step (the accumulating table or, perhaps, packaged into shippers) would require a highly skilled operator or mechanic.

1. Fully Automated Bottling Line

A schematic of a fully automated bottling line is represented in Fig. 5. The major elements are depicted. Sensors to detect miscount, lack of wadding, and improperly positioned caps and ancillary equipment such as bottle blowers and desiccant fillers are not shown. The line can be as sophisticated as desired. Entire automated lines suitable for the clinical packaging area can be purchased.

The various elements are normally arranged in the following sequence; the placement of ancillary equipment is included:

Unscrambling Table Positions bottles for smooth entry onto the conveyor belt.

Bottle Blower (not depicted) Removes any debris that might be present due to the molding process, dust etc. Small extraneous matter can be removed, the diameter of the tubing dictating particle size limitations.

Counter/Filler Either electronic or slat/disc type.

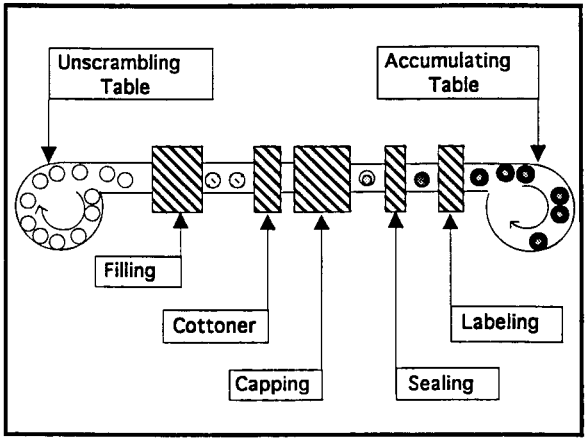

FIG. 5. Bottle line schematic.

Check-Weigher (not depicted) Rejects bottles containing an incorrect fill (by weight) by removing them from the conveyor belt onto a platform. This will ensure a correct fill and is an early warning of problems. The check-weigher must be positioned before the cottoner.

Desiccant Filler (not depicted) Places the desiccant/"odor-eater" into the container. Some prefer to place this before the check-weigher to ensure addition.

Cottoner Places the desired length of wadding into the container.

Sensor (not depicted) Confirms the presence of wadding. Rejects containers missing the wadding.

Capping Places the cap on the bottle.

Sensor (not depicted) Rejects bottles with improperly positioned or missing caps.

Sealing Either induction sealer or "glue-pot".

Retorquer (not depicted) The caps will relax after sealing and should be checked for correct torque. Torque is applied according to specifications.

Labeling On-line labeling using roll stock.

Accumulating Table Accumulates the filled, labeled bottles. Random check can be performed at this time according to the SOP.

When feasible, the on-line labeling using roll-stock is recommended considering the FDA ruling concerning label controls (22). The clinical supplies area is NOT exempt from this ruling. The ruling prohibits the use of gang-printed labels unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color (23,24).

Of the three special control procedures for cut-labeling, only two have application for the packaging area (the third control specifies the use of dedicated lines). The first necessitates the use of electronic or electromagnetic equipment to conduct a 100% examination of the labeling (either during or after the operation). The second option is to have a 100% visual examination during or after the hand labeling operation performed by one person, with an independent verification (100%) by a second person. This regulation has major impact in the clinical area, since cut labels for double-blind studies are usually produced and used.

The FDA states that the above criteria, in conjunction with labeling reconciliation, provide reasonable assurance of labeling control. The ruling also requires that all filled, unlabeled bottles that are set aside for future labeling, be identified. It is not necessary to label each individual container, but diligence must be exercised/demonstrated to prevent mislabeling.

2. Semiautomatic Bottling Line

The semiautomatic bottling line contains some of the preceding equipment online, with subsequent removal of the bottles for manual operations. For example, the automated part could consist of a line with the unscrambling table, filler, and cottoner. The bottle is then removed for manual capping and torque application. Many variations are possible.

E. Blister Equipment for Solid Dosage Forms

The manufacture of medication cards involves two independent processes. Primary packaging, which is the placement and sealing of the dosage form into the blister, and secondary packaging, which is the sealing of the blister units or strips into the printed card-stock. Blister strips are commonly used in OTC preparations, but rarely in the clinical packaging area. Instead, a medication card is used that allows for the printing of instructions, warnings, and caution statements in addition to providing label placement (25).

1. Single-Station/Shuttle Units

The packaging area can manufacture medication cards without resorting to the expense of form/fill/seal equipment by using the single-station/shuttle unit. The single-station/shuttle unit is used for low volume, short runs and allows for the manual placement by one operator of the preformed blister sheet, product, and card. These units require a minimum of floor space. Two tooling designs are necessary, one for the blister filling operation (primary packaging), the other for heat sealing the strips into the card (secondary packaging).

The purchased, preformed blister sheet, is manually filled, lid-stock materials placed over the sheet, and the shuttle pushed under the heat sealing

platen. A two-station shuttle unit has two loading stations requiring two operators. While one is filling, the other is sealing; both use the same heat sealing platen. The blister sheet is then removed, color-coded for identification, and manually cut (paper-cutter) into the desired configuration. Tooling is then switched to that necessary for sealing of the card. The heat sealing process is repeated using the card stock and cut strips.

Shuttle units are available that can seal and cut the preformed filled sheet in one process. In this case, the tooling needed for primary packaging would also contain a series of cutting knives. This method is time-consuming.

2. The Form/Fill/Seal Blister Machine

Many packaging areas are using the more efficient form/fill/seal equipment available. Use of the form/fill/seal blister machine will necessitate the purchase of a heat-sealing unit for secondary packaging.

a. Primary Packaging

The blister operation is unique in that the container (the blister) is formed, filled, identified, and sealed on line. The film is prepared for forming at the preheat station, the softened film is next passed over the tooling, which contains air holes, and compressed air is blown on top of the film forcing it to mold to the shape of the tooling dies. A well-formed blister will have tiny nubbins formed, due to the air holes, on the outer side. The formed film is then cooled, filled with product, sealed to the lid stock, and cut into strips, if appropriate. The seal width around the perimeter of the blister cell should measure at least 3 mm to ensure blister integrity. A schematic depicting the blistering operation for a form/fill/seal machine is shown in Fig. 6.

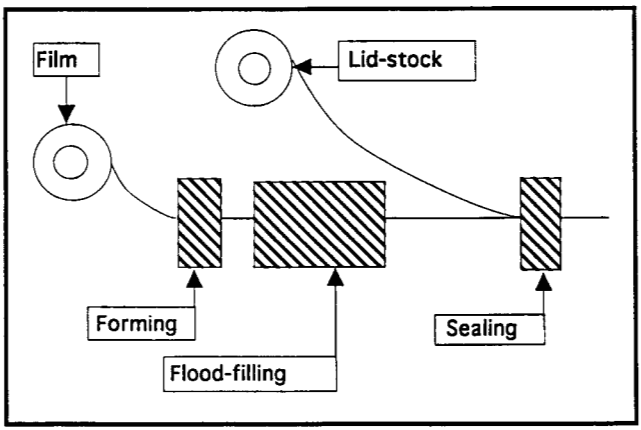

FIG. 6. Schematic of the blister operation.

The machine is indexed the same distance each time. It is important to know this index to prepare the card stock for the blister strips. If a 20 mm index (measured from center to center of two sequential blisters) is used and card stock prepared to hold a strip of 10 blisters, it is mandatory that this 20 mm index be controlled during the entire operation. If the machine index varies, the strip will not fit into the card (the discrepancy is additive along the length of the strip).

Identification of each blister unit by an appropriate symbol is accomplished by either embossing the film or printing on the lid stock. If paper-backed foil is used as lidding, then a hot-stamp printer can be used. This method is clean and involves the use of an ink pad. If foil is used, then liquid ink must be applied. Another method is to use color pens positioned across the web. Identification of the strips is necessary to prevent mixups; all strips will contain identically matched dosage forms for the active and placebo.

Flood-filling is the manual spreading (flooding) of the dosage units over the formed blisters, allowing them to fall into the empty blister. Placement of static-bar equipment is recommended for nonhumidity controlled packaging areas. This will circumvent difficulties during the filling process.

Tooling design is of paramount importance. The blister cavity should be sized to prevent double layering of the dosage form, which results in an incorrect fill.

As the blister strips are manufactured, it is necessary to perform an accurate count, with a check count by a second person. An incorrect count will jeopardize the release of the study. Suppose in the preparation of a mixed card containing one strip of active and one strip of placebo, the count shows that 100 strips of each have been manufactured. If a discrepancy is then noted during the secondary packaging, the question arises of whether an incorrect placement occurred.

The number of strips needed for a study can reach many thousands with many in-process cartons used for storage. Preplanning with regard to the in-process storage in cartons should be considered. The number of strips needed for each product for each treatment is calculated. The strips used for one treatment card are boxed proportionally. For example, if the card design requires one strip of active and two strips of placebo. then the strips are boxed (separately) in a 1:2 ratio. The worst case, due to incorrect count, would be a subsection (the two boxes used) and an investigation can be initiated. After counting, the strips are labeled and stored in the in-process area until they are ready for secondary packaging.

The dimensions of tooling for capsules is of particular importance. The tooling cavity is usually about 1.5 to 1.75 mm longer than the capsule samples sent to the tool and die maker.

The following case history demonstrates how unexpected problems can arise. Tooling was manufactured from samples using placebo filled size "0" hard gelatin capsules from Supplier A. The tooling performed well for many blister runs. Suddenly, the size "0" capsules were sticking to the lid stock and becoming flattened and knurled (due to the design of the sealing station). The film thickness was measured, the dimensions of the blister cavity were determined by an optical comparator, and everything was as expected. Chance conversation with a member of the purchasing staff indicated that hard gelatin shells from Supplier B were now being used due to a pricing incentive. It was believed that a size "0" capsule has definite dimensions and does not vary from manufacturer to manufacturer. This is NOT true. The result is depicted in Fig. 7; the schematic is dimensionally correct (CAD), although not true to size.

The same problem is encountered when interchanging size "0-Elongated" capsules. For other sizes, while the capsule does fit into the cavity and does not protrude, it will not rest on the bottom of the cavity.

During a normal, repeatedly smooth-operating bottle filling run in a production facility, it was suddenly discovered that this time the capsules and wadding did not fit into the bottle. Once again a change of supplier was the cause of the problem.

If the yields on capsule filling equipment are low due to split or improperly locked shells, then the dimensions of the tooling should be checked. The situation is easy to avoid once the cause becomes apparent.

b. Secondary Packaging

Secondary packaging involves the placement and sealing (26,27) of the blister strips in the correct configuration in the medication card. Although the single-station/shuttle unit can be used, most prefer to use a rotary table heat sealing machine. The rotary is more efficient, and also allows for greater control in placing of the strips (Fig. 8).

The number of loading stations depends on the size of the stations and of the table. A table with four large stations (24″ × 36″ sealing area) can be 8

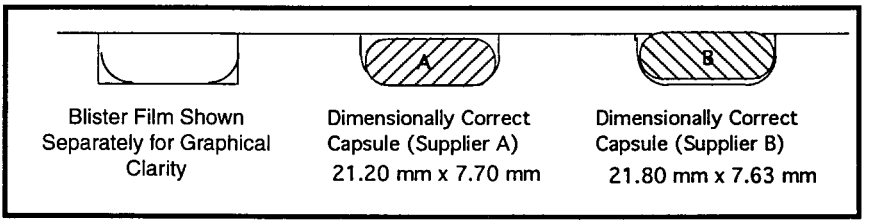

FIG. 7. Schematic showing filled blister.

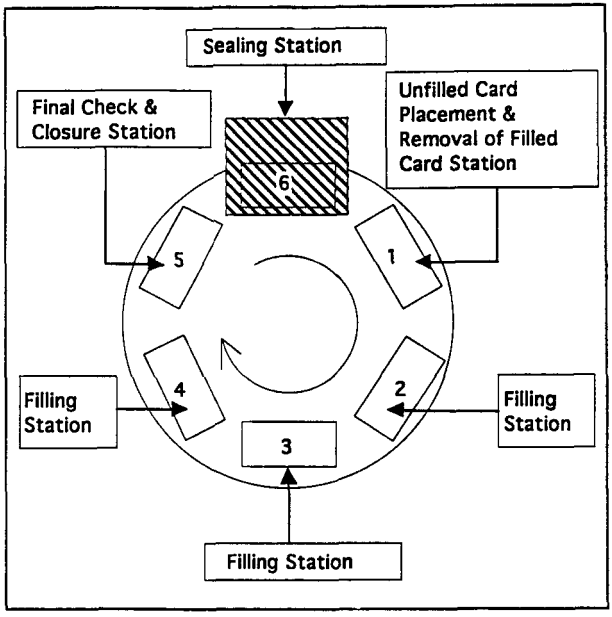

FIG. 8. Schematic of a rotary six station machine.

to 10 feet in diameter and can allow for the sealing of several cards at one time. A six station (12″ × 18″ sealing area) will be smaller in diameter and may accommodate only one card per station.

Although the loading of the strips onto the card stock is done manually, the table rotates at preset intervals. The first station (immediately following the sealing station) is for the removal of the sealed card and the placement of the card stock. The others are for the placement of the strips. A QA check of the filled, open card is recommended at the last station before the sealing station. The card is also closed for sealing at this station.

Operators are positioned at each station (seated or standing) next to a tilt-table holding the boxed strips. The operators decide the timing interval for the rotation of the table.

3. *Manufacture of the Heat Sealing Nests*

Each station of the rotary heat sealing machine has a removable platform (wood or metal) mounted to the table. Usually, the platform is made of laminated hard wood, which is precision machined for flatness. The use of such material, because of its heat transfer and physical properties, is much preferred over other

less costly surfaces. If a metal platform is used, configuration relief openings are present.

The nest, usually made of rubberized or siliconized cork, or rubber, is die cut into the configuration needed and affixed to the wooden board. Most packaging areas prefer to have the nests manufactured by a tool and die maker. However, these nests can be manufactured in-house using a die-cutting, roller machine. The cutting method uses the principle of push-through die cutting. The cutting force is accomplished by applying pressure progressively by means of two contrarotating steel rollers to the cutting edges of steel rule dies. The steel rule die is placed on the feed table, with the material to be cut placed on the knives. A polypropylene sheet is placed on top forming a "sandwich." This "sandwich" is then pushed through the rollers.

The nest design is sent to a tool and die maker who manufactures a steel-rule cutting die. Since the die-cutting machine is of the roller type, the nests must be made up of die cut laminates of cork or other material to prevent skewing of the blister holes. The top layer should be of cork. The stacked nest is held in place and to the board by pressure-sensitive adhesive tape attached to the underside of each laminate. Fig. 9 shows a board and nest and depicts a cross-sectional representation of the nesting materials.

Packaging personnel can easily manufacture six nests in 4 hours. The manufacture of nests in-house is cost-efficient. This capability also allows for more control over the timing needed. When a particular study is completed, the nest material is removed, allowing the boards to be reused.

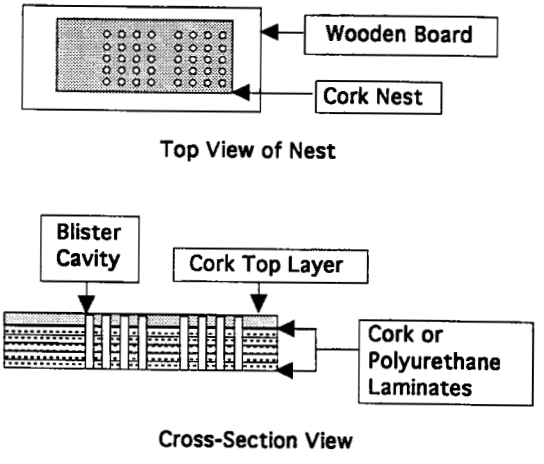

FIG. 9. Schematic showing a nest.

4. Card Design Dimensions

It is important to be aware of the stepwise increase in sizing when planning to manufacture medication cards. The sizing progression is as follows:

1. The dimension of the dosage form is determined.
2. The dimension of the dosage form sets the tooling specifications. As mentioned, the tooling used for forming the blister is usually 1.25 to 1.75 mm larger than the dosage form.
3. The dimension for the blister opening of the card stock is usually 1.0 to 1.5 mm larger than the formed blister.
4. The dimension for the steel-ruled cutting die used to manufacture the nests used for the heat sealing of the blister strips into the card stock is usually 1.0 to 1.5 mm larger than the blister opening in the card stock.

If this progression is considered during the design process, problems involving the width of the bridges (the distance between the openings) for card stock and nests will be avoided. Difficulties during the cutting will arise if the bridge width is too small.

F. Pouches—Solid Dosage Forms or Granular Materials

Two types of pouches are generally used in a clinical packaging area:

1. Purchased plastic pouches with a zipperlike closure. These are available in a myriad of sizes.
2. Pouches that are manufactured, filled, and sealed on a pouch machine. Forming material can be either plastic film or aluminum foil.

Purchased, plastic pouches can be used for preparing a medication card. The dosage form is placed into the pouch, sealed, and then attached to a labeled card. If one is creative, a multidosing schedule can be met by layering the pouches. This is an inexpensive method to prepare a mixed dosing regimen without resorting to the use of several bottles (see Philosophy: Bottle Versus Blister Packaging). The plastic used for the pouches must be protective of the dosage form.

Aluminum pouches may be considered for highly moisture-sensitive materials (e.g., effervescent tablets). The metal pouch is both moisture and oxygen impermeable, thus offering excellent protection. It is often used for the packaging of granular, free-flowing preparations.

The various stages for the formation of a pouch, using a horizontal configuration (Fig. 10) are as follows (28,29):

Folding The film or foil is threaded on rollers that position the material for folding. The bottom of the pouch is the fold.

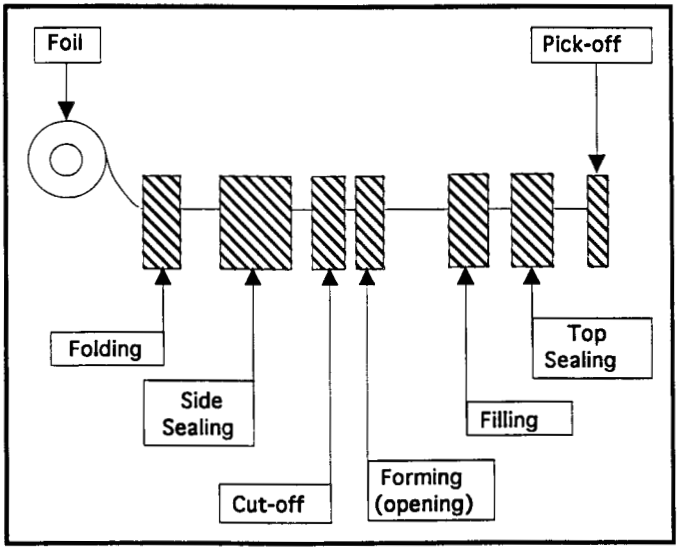

FIG. 10. Schematic of the pouching operation.

Sealing (Sides) The folded material moves through the sealing areas, sealing the material at desired intervals.

Cut-off The folded, sealed material is cut (middle of the sealed area) forming the individual pouch.

Forming (Opening) The pouch is opened to receive the product.

Filling Product is placed into the readied pouch. The fill can be solid dosage forms, powders, or granular material.

Top Sealing The top is sealed. Problems are most likely to occur at this stage. Lack of pouch integrity will usually occur at the corner seals. The destructive method (test pouch is unsuitable for future use) is normally used. (See IN-PROCESS TESTING)

Pick-off The filled, sealed pouches are transferred from the machine onto a conveyor belt.

Checker (not depicted) The individual pouches are weight checked at this point. The conveyor leads to an automated check-weigh station. If the fill does not meet with desired specifications, the pouch is rejected. Weigh checking can also be accomplished manually using a balance. This latter method is obviously more time-consuming.

The finished pouch is then conveyed to an accumulating table for counting, identification marking or labeling, and packing. The vertical configured pouch machine is normally reserved for free-flowing materials (30). Generally, for a

pharmaceutical packaging area, the horizontal configured machine is more useful.

Small semiautomatic machines are available that manufacture pouches of one size. The number of units contained depends on the dosage form dimensions.

G. Liquid Filling

The filling line for liquids (solutions, suspensions, and elixirs) utilizes a similar setup to that for solid dosage forms (Fig. 11). Two separate lines should be used. The function of the unscrambling table, bottle blowers, sealing station, retorque station, labeling station, and accumulating table has been described (see Automatic Bottling Line).

A wide selection of pump types is used for filling (31). Step-filling allows for filling of larger volumes or of more viscous suspensions without resorting to production size equipment. Two peristaltic pumps are used. If the amount to be filled is 120 ml, the first pump will dispense 55 to 60 ml, with the second completing the fill.

If the bottle calls for a dropper assembly, induction sealing cannot be used. Usually it would be better to seal the bottle and include the dropper assembly (protectively wrapped) in the final carton.

It is good practice to use new tubing for each fill. Tubing can be cleaned, but the possibility of objectionable microorganisms is an ever present danger. Microbial growth is supported by the very nature of most pharmaceutical liquid preparations.

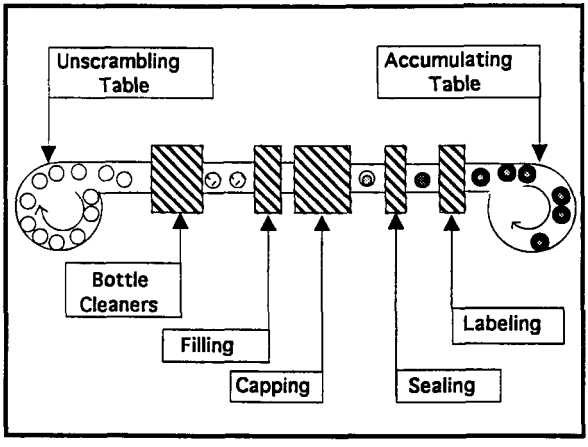

FIG. 11. Schematic for liquid filling operations.

Unlike solid dosage forms, which tend to be fairly rugged with respect to handling, liquid products are more prone to contamination. Consequently, great care must be exercised in the processing and packaging operations. Specifications for liquid products usually require that microbiological testing be performed.

In dealing with high viscosity suspensions, it is important to differentiate between "amount filled" and "amount dispensed." Suspensions will adhere to the walls of the container (wall cling), decreasing the amount available. For example, if the protocol calls for dispensing 15 ml four times, the dispensing of one 60 ml bottle may be insufficient. It is also necessary to allow head space for adequate shaking. The difference may not be noticed if the patient is using a spoon as the measuring device. If a calibrated syringe is to be used, however, it would be wise to dispense a second bottle, or increase the size of the bottle (e.g., 6 ounce) if there are supporting stability data. Samples must be collected from the beginning, middle, and end of the run for testing (e.g., content uniformity, viscosity, and pH testing for suspensions).

H. Packaging of Semisolid and Gel Preparations

Except for the manual filling of a small quantity of tubes, this process is usually performed by a contract packager. The plastic or plastic laminate tube is widely used mainly because of its resistance to attack by the product and to air, odor, and light. This type also offers more potential for graphics than does the metal (aluminum) tube.

Dispensing can present a problem. The use of measuring tape, "round spot" spatulas, and other equipment to ensure the exact amount needed for effectiveness is very subjective. The amount applied, following instructions to place a 1-inch ribbon of material on the arm, can vary greatly, depending on the manipulations performed during squeezing. For this reason, many packagers are now including a metered dose cap for exact application.

VI. IN-PROCESS TESTING

The cGMP requirements state that written procedures be established describing the in-process controls needed to ensure integrity of drug products. It is not enough to perform the testing; documentation must be provided.

The tests listed below are for certain operations (32). The in-process controls for correct counts and other variables are not included.

A. Testing of Film Used in the Blister Process

The orientation of the film in contact with the product can be easily determined. It is necessary to perform the testing when placing the roll on the machine and subsequently before and after each splice.

Film is manufactured in widths suitable for production machinery and hence is much wider than that used in the clinical packaging area. Rolls of film for clinical packaging use are usually spliced cuts from these larger production rolls. It is wise to request that no more than four or five splices be present in a roll of 12 to 14-inch outer diameter (OD).

The correct positioning of the roll, based on stability data, is necessary at the onset of the operation to ensure that the correct side of the laminate is in contact with the drug product. Then testing at the splice is necessary to ensure that the film has not been reversed. In some instances, a reversal has occurred. Results of the testing are documented on the run sheet.

1. Morpholine Test for PVDC

This test is quick and easy to perform. Several drops of morpholine are placed on both sides of the PVC/PVDC laminate. A brown discoloration will occur on the PVDC side. The PVC side will not be affected in the same manner, although a very slight cloudy image may be seen under close inspection.

2. Methyl Ethyl Ketone (MEK) Test for Aclar

This test is similar to the preceding test, except the Aclar side remains clear. The PVC side, after wiping off the MEK, will either become cloudy or appear scratched. Tetrahydrofuran (THF) can also be used as the test reagent.

B. Blister Integrity Test (Destructive)

This test is commonly called the leak test. A bell jar is partially filled with colored water. The blister units or strips to be tested are placed under the water (the desiccator plate can be used to keep them submerged) and a vacuum established. If there is a lack of integrity, the colored water will enter the blister upon the release of the vacuum. The blister seal should measure a minimum of 3 mm to ensure integrity.

When this test is performed, strips comprising the entire width of the web must be evaluated. It is good practice to perform the testing at the beginning of the operation, at timed intervals during the run, and after completion of the run. Results are documented on the packaging run sheet (time, result, initials of operator performing the test).

C. Pouch Integrity Test (Destructive)

This test is commonly called the bubble test. The pouch is placed under water, and compressed air is forced into the pouch via a needle. A small piece of tape is normally placed on the pouch at the point of puncture. If the pouch seal has been compromised, bubbles will be noticed emerging from the "bad seal" area.

If seal integrity (blisters or pouches) has been compromised, it is necessary to test backwards to the start of the problem. For this reason, a record of when the units were completed, or at least the order in which they were completed, must be maintained.

D. Torque Test for Bottle Closures

In addition to visually inspecting the inner seal (e.g., presence of, correct positioning) of the bottle, one must check that the correct torque, according to department policy, has been applied to the cap. A torque tester is used. The test is dependent on the technique used by the operator; therefore, it is most important that training procedures be implemented to ensure uniform methodology.

VII. LABELING

This section discusses the controls needed for the application of the label to the container. As previously indicated, 100% verification of the labeling by two independent operators is required. The label text should be checked for accuracy before entering the labeling room; the second check can be on the labeled product.

The application process should be accomplished with dividers separating the different operators to prevent mixups. If possible, a separate area of the room should be used. Many facilities are now designed with room dividers (e.g., one large area can be divided into smaller areas).

The unlabeled product is brought into the area, and it is verified that it is the desired product. The required number of containers is allocated, and the rest is removed from the area. This provides a check at the end; there should be no surplus of either component (e.g., unlabeled containers or unapplied labels). If the patient is to receive several containers of the same product, it is convenient to place them into packers at this point. The packer is then labeled top and front. Documentation for the checking, receiving, labeling, and reconciliation is recorded. The labeled product container is then removed to the in-process area awaiting assemblage.

Labels should be applied in the same position each time. If one operator places the label higher than another operator, it may be perceived by the patient as being two different drug products. It is helpful to use the seam of the bottle for label positioning. In the case of medication cards, a schematic can be used showing the desired positioning for all labels and defining the placement for the printed label indicator markings (Fig. 12).

The labeled product is submitted for final identification testing. This involves analytical testing to ensure that the correct product is in the correct

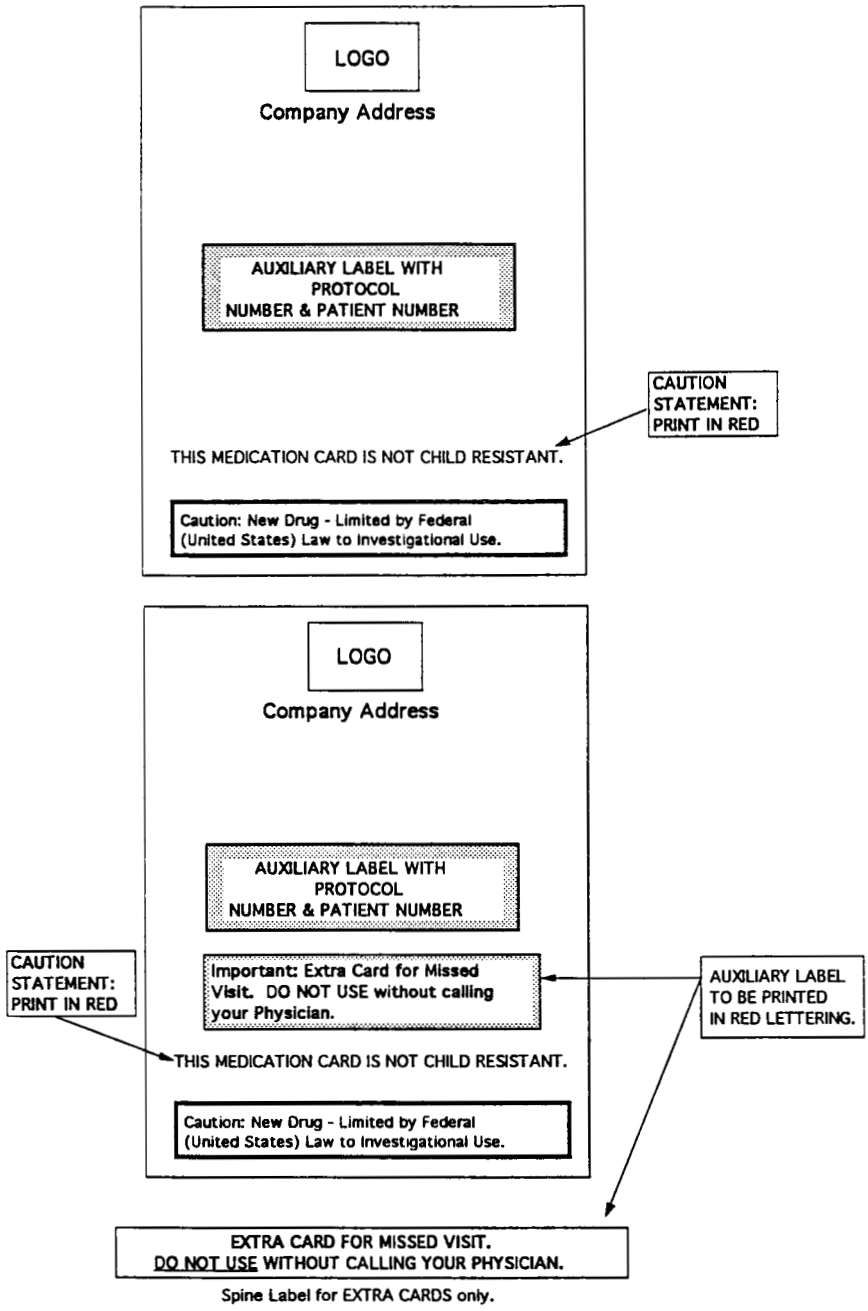

FIG. 12. Front panel for medication card showing auxiliary labeling.

container. In the case of medication cards, each blister unit (or strip containing all the same product) is tested for correct placement.

VIII. ASSEMBLAGE

The assemblage or collation operation is the final packaging step. Each assembly must be tailored according to its complexity. An uncomplicated, open study containing one package size and one label design would require considerably less resources and checks and balances than one with more treatments, titration schemes, study visits, rescue medications, etc.

The method used for an open study is straightforward. Unless the study indicates the use of patient numbers, there is no need for repeated checking. Verification of the correct drug product, correct labeling, and correct number per correct shipper is all that is needed. For a large, double-blind study, all of the labeled products are brought into the area and placed conveniently around the area for ease of retrieval.

Collation for the closed packer (Figs. 13 and 14) is planned as follows. Two long tables are abutted to each other perpendicularly in the center of a large room. The skid holding the unassembled packers is placed on the floor at one end of the table. Another skid holding the unassembled shippers is placed at the other end, along with taping materials and the shipper labels. The labeled drug products are brought into the area and verified. The study is assembled "last patient first." The first operator takes an unassembled packer, applies the packer label (easier to apply when the packer is in the flattened state) containing the protocol number, patient number, and so forth; covers the label with clear tape to prevent possible smearing or damage during subsequent handling; and constructs the packer. The next operator, using the schematic as a guide, positions the dividers and the cardboard inserts. Since the study calls for different size bottles, the next two operators place the "Up-Titration"* (two levels apiece) portion into the packer. The next operator checks this work and then places one level of the "Maintenance/Down-Titration"† portion. The next two operators complete this portion. The next operator checks each bottle (final check) and closes the packer. Meanwhile, the shippers are being assembled and labeled. Each shipper holds five packers. The five packers are placed into the shipper, checked to ensure that the correct packers are being placed into the correct shipper, and are taped shut. The shipper is placed on another skid. Since the first shipper completed contains the last five patients, the skid will be stacked

*Up-Titration: Planned, consecutive dosing using an increasing dosage schedule.
†Maintenance: application of a constant dosing schedule.
Down-Titration: Planned, consecutive dosing using a decreasing dosage schedule.

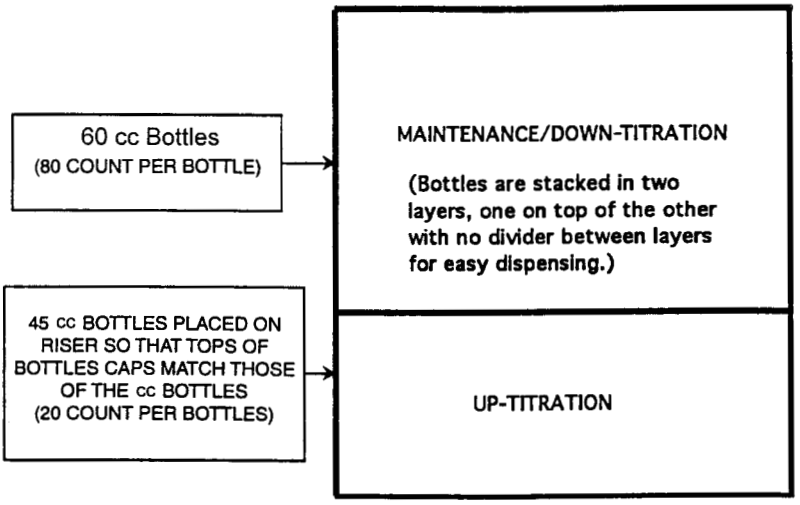

FIG. 13. CAD schematic of closed packer.

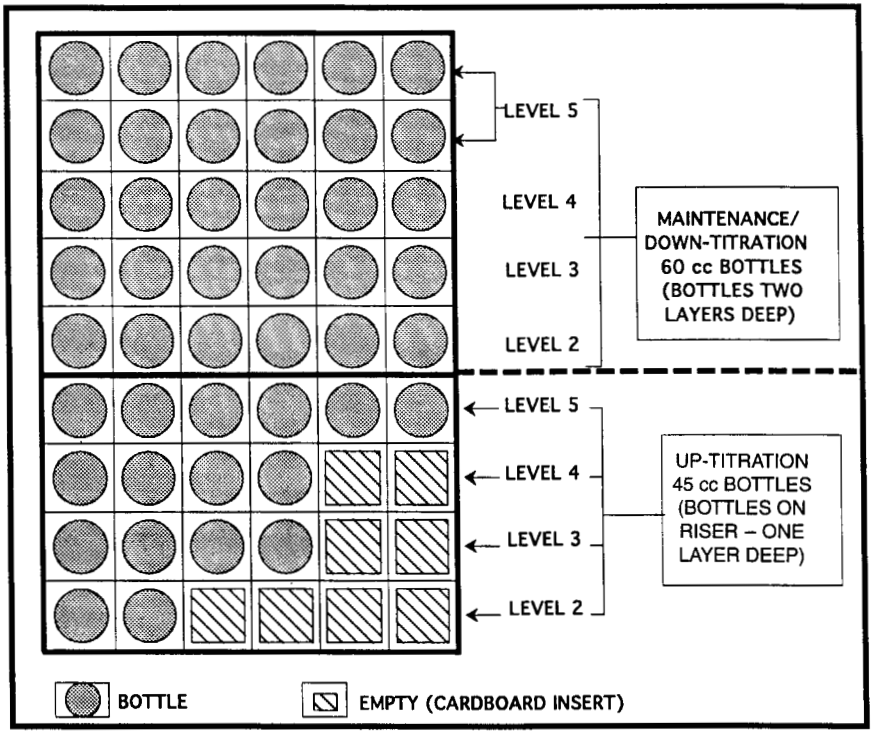

FIG. 14. CAD schematic of final pack-up into shipper.

in proper request order. Supplies were needed for more than 400 patients taking part in a 1 year, double-blind, multicenter study. Assemblage will require less than 1 day to complete, using 10 operators.

The preceding example illustrates several factors: the need for planning and for repeated checking by more than one individual, which in turn show the sharing of responsibility for the integrity of the study. A clinical packaging area operates in a "zero defect" environment. It is very easy to degenerate into a "finger-pointing" atmosphere based on who initialed the documentation.

Teamwork, or rather team spirit, must be encouraged. The operators planned the preceding assemblage, and each believed his or her own part was just as important as that of the others. When an error is discovered, it must be met with a feeling of relief, in that it was discovered before leaving the packaging area. Manual labeling and other operations can be extremely tedious. It is important to foster a feeling of pride for a "job well done."

When a study is assembled, it is efficient to consider the block size* and how the way in which the clinician is planning to ship to the sites. If two blocks are shipped to each site, it is timesaving to place the patient supplies for the two blocks into one shipper. The shipper can then be stored awaiting shipping orders. This also allows for the designing/purchasing of custom shippers "to fit." No filler (environmental consideration) is needed.

IX. DOCUMENTATION

Throughout the entire packaging process, all operations are conducted under cGMPs, using procedures described in the SOPs. Documentation is constantly being gathered, and all records must be compiled in the packaging dossier for review by a compliance function before release for clinical shipping.

Typical documentation included in a dossier would consist of job work orders for each operation, packaging, labeling and assemblage run sheets, clean equipment and room checks, the signing of equipment and room logbooks, operator training documentation, supporting stability data, component specifications and release verification, final protocol, request for clinical services forms, final testing of labeled product results, testing of assembled product results, microbiological testing results (if applicable), and expiration dating. All of this is necessary to obtain the Release for Human Consumption document, the final affirmation that the study has been processed according to the standards required.

*In a randomized, blinded study, the block size is statistically determined to ensure that each site receives an equal number of patients in each treatment group or sequence.

X. TRAINING

The training of personnel is a critical step to ensure that a quality package is prepared for the investigatory study. Each member of the team must be qualified and capable of performing and understanding each assigned task (33).

Section 211.25 of the Code of Federal Regulations (34) states:

> Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience or any combination thereof to enable that person to perform the assigned functions.
> Training shall be in the particular operations that the employee performs and in current Good Manufacturing Practices (cGMPs) . . . and written procedures required by these regulations as they relate to the employee's functions.

A Clinical Trial Materials Training Guide is available from the ISPE (35). This guide is a valuable resource and should be used in conjunction with mentoring by the supervisor.

XI. SUMMARY

This chapter has presented an overview of the unit functions and physical components of a clinical packaging operation, their impact on the quality and compliance of the final product, and the effect of scheduling and planning on day-to-day operations.

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10

Quality Control

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I. INTRODUCTION

This chapter reviews philosophies and strategies for quality control applied to the manufacture of drug substances and drug products used in clinical studies worldwide, taking into account different regulatory requirements applicable. Furthermore, the impact of the evolving nature of the development process as projects progress from phase I to phase III and the scientific challenges associated with drug substance synthesis, drug product manufacture, and determination of stability characteristics are discussed. Although not a critical issue for line extension developments, rate of failure has a major influence on those companies developing new chemical entities (NCEs) where as few as 1 in 10 compounds could progress from preclinical development past phase II into phase III. With this high technical risk, there is obvious pressure to phase effort applied as a function of risk. Throughout the chapter, some indication of the extent of work that could be performed at each stage of development is given.

The European definition (1) of quality control is "that part of good manufacturing practice (GMP) which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures . . .", and broadly, this definition applies to the U.S. current Good Manufacturing Practice regulations (2).

Throughout the chapter, reference is made to the regulated environment including manufacturing and control information, which must be filed on a product-by-product basis with regulatory agencies, and regulations that must apply to facilities and procedures used to perform quality control work.

A potential supply chain to produce drug substance and drug product is summarized in Fig. 1 and briefly discussed below. Quality control of packaging operations is reviewed separately in Chapter 8.

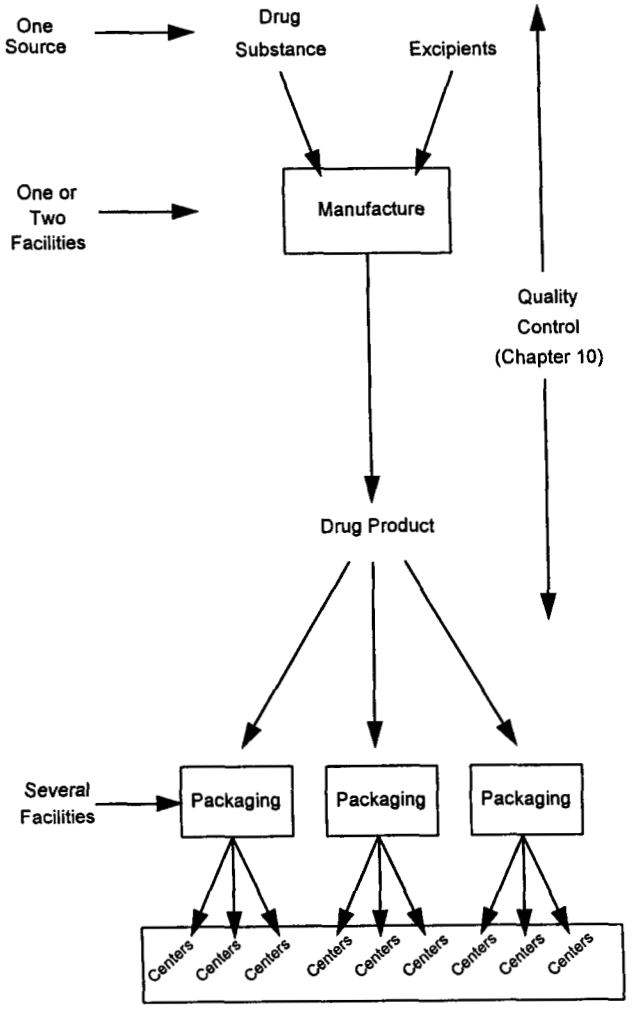

FIG. 1. Typical chain of manufacture and packaging for supply of clinical studies worldwide.

Owing to the need to have specialist costly chemical manufacturing facilities often requiring dedicated environmental controls, it is rare for companies to manufacture drug substance in more than a single supply chain, although, because of the number of synthetic stages, it is possible that either more than one facility within an organization or a third party could be used for individual stages. Controls are normally exercised on contributory (contribute to molecular

skeleton) and noncontributory (e.g., solvents, reagents) raw materials, and any intermediates, as well as the drug substance itself before drug product manufacture.

The extent of control in terms of methods and limits applied and degree of validation of analytical methods, depends on stage of development, tests, and limits included in regulatory submissions, most notably Investigational New Drug Applications (INDs) in the United States, and on company policy.

Specialist drug products used in clinical studies, for example sterile products and metered dose inhalers, which require dedicated facilities, are also probably manufactured at a single site, and quality control is applied during manufacture and by testing resulting drug product. Solid dosage form manufacture could be performed in more than one facility, most typically one sited inside the United States to facilitate supply to the geographical area where many important clinical studies will be performed, and one sited outside the United States, (e.g., Canada or a European country) to facilitate supply to the rest of the world. Again, third party facilities for manufacture of specialist drug products (e.g., sterile lyophilized products or metered dose inhalers) are often used. As an integral part of the drug development process, quality control must evolve as more information relating to a drug substance and drug product becomes available, so that at the end of development, controls can be finalized for incorporation in Marketing Authorization Applications (MAA) and New Drug Applications (NDA) and manufacture of commercial products following regulatory approval. Furthermore, the development process itself within individual companies is changing due to the impact of the obvious desire of companies to develop drugs faster in the face of relatively new, but important cost pressures. Layered on top of these pressures is the impact of regulatory changes, for example, harmonization of regulatory requirements at the NDA/MAA stage, certainly in terms of stability studies and specification setting for impurities. Of these two topics, specification setting for impurities has most relevance to standards for quality control of drug substance and drug product during development.

Finally, all manufacturing and control information relating to batches of drug product used in clinical studies, which are included in NDAs/MAAs, must be considered inspectable by at least one of the world's regulatory agencies, although the extent and mechanism by which this verification of authenticity occurs depend on the agency. As part of Pre-Approval Inspection (PAI), it must be expected that the United States Food and Drug Administration (FDA) will investigate and inspect, manufacturing, and control records for batches of product used in "critical" clinical studies, which currently could be interpreted as phase III studies referenced in the NDA, and the so-called Biobatch, where a batch of drug product is manufactured at commercial or commercial-representative scale and tested for bioequivalence with a lot used in a critical clinical

study. Similarly, the Japanese Ministry of Health and Welfare (MHW) could request copies of manufacturing and control information of batches used in critical Japanese clinical studies.

II. DEFINITIONS

Nomenclature in this chapter is based on current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals given in Section 211 of the Federal Register (2), definitions for Section 211 being given in Section 210.3. Nomenclature in the European Guide to Good Manufacturing Practice for Medicinal Products (1) and in Europe generally has some differences, and to assist readers a comparison glossary is given in Table 1.

Both these publications refer specifically to drug product manufacture. However, Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act in the United States requires that all drugs be manufactured, processed, packed, and held in accordance with cGMP; and accordingly the FDA has produced a Guide to Inspection of Bulk Pharmaceutical Chemicals (BPCs) (3) where essentially the same terminology is used for drug product and drug substance, except for the introduction of the phrase "bulk pharmaceutical chemicals", which are usually made by chemical synthesis, by recombinant DNA technology, fermentation, enzymatic reactions, recovery from natural materials, or combinations of these processes.

Phase I, II, III, and IV clinical studies are defined in Table 2, although it is recognized that some companies apply subdivisions of some or all of these phases.

TABLE 1 Glossary

United States	Europe
Drug substance	Bulk drug
Drug product	Bulk product (not packaged) Finished product (packaged)
Component	Starting materials Packaging materials
In-process material	Intermediate product
Master production and control record	Master formulae, processing, and packaging instructions
Batch production and control record	Batch processing records Batch packaging records

TABLE 2 Definition of Phases I, II, III, and IV

Phase	Definition
I	Safety and pharmacokinetic studies often in "normal" patients involving ascending single dose, and multiple dose studies. Bioequivalence studies including comparison of a dosage form to a reference formulation, typically a solution or suspension (Relative Bioavailability), comparison of a dosage form to an intravenously administered dosage form (Absolute Bioavailability). Special studies to examine, for example, the effect of food, antacids or drug-drug interactions, and to determine any changes in pharmacokinetic performance in special groups such as renally or hepatically impaired patients.
II	Dose ranging studies in patients, which may or may not be comparative, to determine an efficacious and safe dose for an indication.
III	Long-term, controlled studies in patients to confirm safety and efficacy in an indication, these studies often being blinded and comparative with other therapies.
IV	Studies performed post approval to define further relative safety and efficacy in wider patient populations; these studies are often comparative, but may not be blinded.

As indicated in the Introduction, a good definition of quality control is given in the European GMP Guidelines (1) and is quoted in full here:

> Is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

This definition also covers the responsibilities of a Quality Control Unit defined under Section 211.22 of the Federal Register (2).

Many companies have so-called Quality Assurance Units, which could be regarded as subgroups of the Quality Control Unit, with responsibilities, for example, of document review (both laboratory and production records), confirmation of compliance with filed INDs, and final release for intended purpose. The function of this type of Quality Assurance Unit should not be confused with the wider definition of quality assurance as given in the European GMP Guidelines (1), which derives from the U.K. Guide to Good Pharmaceutical Manufacturing Practice 1983 (4). Quality assurance, according to the broader definition, "is the sum total of the organized arrangements made with the object of ensuring that products will be of the quality required for their intended use. It is Good Manufacturing Practice *plus* factors outside the scope of this Guide (such as original product design and development)."

Compliance is the need for production and laboratory records to be consistent with manufacturing and control information filed in IND and/or Clinical Trial (Exemption) (CTX) applications. Proposed changes must be filed with regulatory agencies. Additionally, facilities and procedures must comply with guidelines and regulations for good manufacturing practice, for example, U.S. Code of Federal Regulations (2).

III. REGULATORY BACKGROUND

The regulatory background to clinical supply manufacture and control can be divided into:

Regulations/guidelines applying to procedures and facilities
Inspection of records, operations, and facilities
Manufacturing and control information filed with agencies.

All these issues have a significant impact on quality control procedures and laboratory operations.

All quality control work, procedures, and facilities will depend on a company's interpretation of regulatory requirements. The current regulatory situation is summarized, followed by pragmatic approaches taken by many companies, and finally some thoughts relating to the future.

A. Current Situation

The FDA has stated (5) and industry understands that cGMPs (2) apply to manufacture and control of clinical supplies used in studies performed in the United States, or included in NDAs. The FDA (5) has issued a guideline to allow some interpretation of Parts 210 and 211 of the Code of Federal Regulations (2) on the preparation of clinical supplies for use in IND studies. Additionally the European guidelines (1) indicate that the principles of GMP apply to preparation of products for use in clinical trials. Guidelines have been published by the Japanese MHW (6) to provide guidance on facilities, and manufacturing control and quality control standards for investigational drugs used in clinical trials from phase I onwards.

Clinical trial regulations differ widely among territories and as a result, chemistry, manufacturing, and control (CMC) documentation filed with regulatory agencies differs greatly in terms of content, amount of information, and most importantly, style (see Chemistry, Manufacturing and Control (CMC) Documentation Filed with Agencies).

Only the U.S. FDA is likely to inspect facilities or current laboratory information pertaining to clinical supply manufacture during the course of studies before filing an NDA/MAA, but inspection of facilities and clinical trial manufacture and control documentation as part of the NDA approval process is now almost guaranteed as part of the FDA's PAI program. These FDA in-

vestigations are designed to determine authenticity of data included in NDAs and absence of "fraud" and additionally examine compliance of clinical trial manufacturing and control facilities and procedures with cGMPs.

The Japanese MHW could review documentation as part of their Good Clinical Practice (GCP) examination or examination of manufacturing and control reports during Japanese New Drug Application (JNDA) review.

B. Typical Approach

1. *Regulations/Guidelines for Procedures, Facilities and Inspection* (3 head?)

As indicated previously, the FDA expects, for clinical manufacture, compliance with cGMP regulations as applied to commercial products (2), with suitable interpretation and minimum difference. When performing PAIs, companies should expect FDA investigators to investigate quality control facilities and procedures that have been used to release critical clinical batches including the Biobatch. Clinical supplies for the United States, therefore, should be controlled in compliance with cGMPs. Not to comply with these regulations brings a risk of a nonapprovable NDA with accompanying business implications.

In Japan, GMP regulations (6) relating to facilities and procedures manufacturing clinical supplies have been issued. Compliance with U.S. cGMPs will also allow compliance with Japanese GMPs, although organizational responsibilities are defined differently for Japan as compared with Europe and the United States.

In Europe, the principles of GMP apply as detailed in the Introduction to the Guide to Good Manufacturing Practice for Medicinal Products (1). Although the strength of wording and legal positions of U.S. and European regulations are different, in practice, compliance with U.S. cGMPs will meet European requirements.

In summary, compliance with U.S. cGMPs is required to obtain approval in the United States, and with little modification, these procedures are acceptable in other territories.

2. *Chemistry, Manufacturing and Control (CMC) Documentation Filed with Agencies*

It is not intended here to give details of regulatory requirements for different territories, or to work through an example of a U.S. phase III IND, which contains the most comprehensive information at the clinical trial stage. To compile an IND, the reader must refer to the guidelines (7) and take advice from a regulatory expert. FDA has produced revised guidelines with the aim of reducing the amount of information required in phase I INDs (8).

Since a phase III IND must contain a comprehensive amount of control information, this information could be used as the basis of a "dossier" for each

compound, which will serve as a basis for a future NDA submission. A phase III IND must contain:

Evidence of chemical structure
Specification and methods for drug substance
Specification for raw materials used in drug substance synthesis
Specification and methods for drug product
Drug substance and drug product batch analysis
Drug substance and drug product stability data
Characterization of reference material

Both the FDA and the U.K. Medicines Control Agency (MCA) have revised their requirements for Phase I IND's (8) and CTX submissions (9), respectively, such that phase I INDs are a summary of information and could contain the same information as a CTX.

For an organization manufacturing clinical supplies in the United States for export to another country for use in a clinical study, the company must have either a filed, open IND for the drug, or must comply with U.S. Export Exemption regulations (10). Both routes of export from the United States require additional effort and documentation compared with manufacture outside the United States and in the case of use of the IND procedure, U.S. compliance issues arise.

C. Future

It is probable that there will be a consistent European clinical trial approval system and more formal inspections—the equivalent of PAI. It is also likely that definitive Japanese requirements will emerge for clinical trial approval, probably equivalent to U.S. INDs. It is hoped that these will be harmonized, without additional requirements to those currently applied in the United States or Europe, obviating production of a third set of clinical trial application documentation.

The European GMPs require that release of products for sale should be performed by a "Qualified Person" (11), a person with the accredited professional qualification. In response to industry comments, however, it appears that release for clinical trials could be performed by a suitably qualified person or persons with appropriate training, but not necessarily having "Qualified Person" status.

IV. ORGANIZATION, PERSONNEL, AND TRAINING

Experience of many years of clinical trial quality control work indicates that selection, development, and above all training of personnel are key to a successful operation.

A. Background

The development environment is much more demanding that a manufacturing organization, there being greater chance of facing new situations and more changes due to scientific or project pressures. Within the totality of a development quality control organization, there must be opportunities for expression of:

Innovation
Good science
Previous experience and knowledge
Responsiveness to internal customer requirements

At the same time, the quality control organization must remain compliant with the company's interpretation of regulations. These characteristics are very rare in any one individual, with the result that different companies, operating with different histories, under different pressures, and in different cultures, have different organizations to deal with their particular requirements. It should also be noted that regulators place a high priority on personnel issues, U.S. cGMPs including as the second section Subpart B - Organization and Personnel, and the European GMPs having Personnel and Training as Chapter 2.

B. Typical Organizations

Some examples of different types of organization of analytical chemistry departments are given here, although it is common to use a blend to suit a particular company structure. It is rare for organizations to remain static since they must change to meet new challenges and needs, and possibly to fit new personalities, and perhaps cultures, following, for example, a merger. Analytical chemistry departments are often the function within which quality control responsibilities lie, or indeed the department could be the quality control unit within a development organization. Analytical chemistry departments could be organized as:

- project based, either within the analytical chemistry department or integrated into other disciplines
- function based, with method development separate from method application, which may or may not be divided into stability testing and quality control
- technique based. This structure is often used for high-cost spectroscopic techniques, such as nuclear magnetic resonance (NMR) and mass spectrometry (MS), and microbiology.

Whatever organization a company uses to define the quality control unit, an increasing number of organizations have a separate "Quality Assurance Unit" with many of the following responsibilities:

Approval of standard operating procedures (SOPs)
Approval of methods
Approval of specifications
Review of batch production and control records
Release/rejection of batches for packaging
Release/rejection of packaged clinical supplies for despatch to clinical centers
Investigation of complaints and after recalls
Performance of internal "compliance" audits
Transcription and authenticity check of CMC data submitted in regulatory filings.

This unit reports to the head of the quality control unit, or perhaps to a more senior individual.

C. Training, Selection, and Development

Training of personnel is critical to ensure that a quality control unit exercises its duties fully, efficiently, and in compliance with procedures laid down by management. An individual must receive training in particular operations and in current GMP, applied by that particular organization. Training must be continued, particularly when individuals have not performed an operation for a period of time, and when there are changes to procedures, no matter how minor. Training should be performed using written programs, these programs including reference to SOPs but desirably extending to include "nice-to-know" background information, which allows training in particular procedures or cGMPs to be placed in appropriate perspective. Effectiveness of training should be monitored. In practice, this requires asking individuals to perform predefined exercises to generate known results, or to be able to ensure trainers by written or verbal means that they have understood the training given. Finally, records of training should be maintained, which should document not only that training has been delivered by a trainer, but also that it was received and understood by the individual.

Selection of individuals is also important to an organization since new individuals must not only have obvious technical competencies, but also must have other competencies to contribute to the total organization. These competencies include innovativeness, flexibility, thoroughness, attention to detail, and ability to follow procedures.

In the modern, western competitive environment, many candidates look beyond the job for which they are being interviewed and expect answers to their questions about how the job may develop, or availability of opportunities to further their careers. Management must give these development issues thought and be able to provide credible answers.

Whatever organization is used, staff must be clear about their responsibilities and accountabilities, which should be presented in writing in the form of job descriptions and supported by written procedures. These procedures must detail either management levels or actual individuals responsible for authorizations and approvals.

V. PHILOSOPHY OF QUALITY CONTROL FOR WORLDWIDE CLINICAL SUPPLY

Multinational companies with widely different histories, cultures, organizations, and location of manufacture should be expected to use a wide range of strategies to source worldwide clinical supplies. Indeed, different approaches could be taken by a single company depending, for example, on location(s) and size of a particular trial, project status within the company, available resource within the company, and comparator to be used. Nevertheless, companies are evolving some high level strategies and philosophies to manufacture and control clinical supplies for worldwide trials. These include the following elements:

Science
Troubleshooting
Interface with development process
Phasing of drug substance scale up
Selection of formulation
Microbiological testing
Compliance of components with pharmacopeias
Limit setting, use of in-house versus regulatory limits, and changes to limits
Use of certificates of analysis and third party analysis
Establishment of regulatory limits and methods for filing in commercial product NDAs and transfer of this technology to manufacturing sites. This issue is beyond the scope of this chapter.

A. Science

Quality control units historically have a reputation for being good at routine work, but unimaginative, lacking in scientific thinking, capability, and innovation. Within the quality control organization, characteristics such as carefulness, thoroughness, attention to detail, and excellent documentation must exist; but

alongside these, there must also be sufficient scientific ability to be able to talk meaningfully to and command respect from process chemists and formulators.

Close interaction is required between analyst and process chemist, particularly in the phase of design of optimum synthetic route, when identification of impurities and theoretical evaluation of reactions to speculate on potential impurities are important requirements, allowing the process chemist to alter or optimize choice of synthetic step or reaction conditions to reduce impurities. Use of spectroscopic techniques, such as NMR and mass spectrometry is mandatory. These techniques are applied to products of reactions either on their own, or in tandem with a separative technique such as high performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas liquid chromatography (GLC), capillary electrophoresis (CE) or supercritical fluid chromatography (SFC). Using information obtained from these identification studies, analytical methods can be developed on a rationale basis, applying the most appropriate technique rather than the classical approach of examination of reactants empirically using the analyst's favorite chromatographic procedure, with modifications, to try to establish "what is present." Routine application of empirically developed methods understandably gives analysts a poor scientific reputation.

Many drug substances are now developed as single enantiomers even when there is more than one stereogenic center. Consequently, a detailed knowledge of stereochemistry, stereoselective reactions, and stability of resulting stereogenic centers is required.

It is obviously most efficient if analytical methods for determination of degradation products in drug substance, and in drug product, are based closely on those developed for determination of organic impurities in drug substance. Again scientific knowledge is required about drug degradation pathways and rates of degradation under different conditions in solution, and solid phase, or in the case of some types of drug products (e.g., suspensions, creams, aerosols) in heterogeneous phases. Experience shows that close interaction with formulators is required when performing compatibility studies, or preliminary accelerated stability studies on prototype formulations.

When developing final methods, which ideally should be completed before phase III clinical studies commence, rigorous analytical science must be used to develop methods that have appropriate accuracy, precision, specificity, limit of quantitation, and most importantly are robust. With the drive by most multinational companies to operate the same method in all commercial manufacturing sites worldwide, methods developed before phase III commences have to withstand the following rigors:

Time: Methods have to be applied to clearance of clinical batches and to stability samples over a minimum of about 2 years in a single develop-

ment laboratory. Chromatography columns will change, as will analysts during this period.

Transfer to manufacturing quality control laboratories. Greater stresses are placed on methods transferred to other facilities, particularly those operating in other countries. Column packings and suppliers are never quite the same as the original, solvent quality varies, and there are always differences in interpretation of written analytical details by analysts in a different laboratory, which could produce systematic, unacceptable differences in performance of the method.

Consequently, a structure approach to method development is required, using experienced analysts and computer-based statistical experimental design and optimization packages.

Although change of method right up to the date of filing an MAA/NDA is possible, there are penalties in terms of redevelopment and validation resources, the need for correlation data between methods, and the resulting untidy regulatory package, which makes the reviewing chemist's job harder. Late changes of method always have the potential to generate "new" impurities, that is, impurities that may not have been totally resolved by a previous method. Observation of these so-called "new" impurities inevitably leads to additional work under intense management pressure to establish whether this impurity is qualified and was present in previous batches, and most importantly, in batches used in toxicology studies.

In summary, development of a robust method, meeting all validation criteria, must be a rigorous exercise based on sound scientific principles, using studies designed to stress the method and hence determine the boundaries of operability, so that it can be operated over a relatively long period of time (many years), in different analysts' hands, often in other countries, and in several laboratories, with a variety of equipment manufacturers, and different sources of consumable materials. This task cannot be performed empirically.

B. Troubleshooting

Quality control work has a high potential to identify problems with manufacture of drug substance or drug product. Examples are well known to those in the field, and there is no such thing as a "normal" problem. Common problems found during development are the following:

1. Drug Substance
   New organic impurity above 0.1% w/w or significant change in impurity profile
   Residual inorganic impurities outside specification
   Unacceptable subjective appearance

High residual solvent levels
Assay out of specification for the required salt form
Observation of a new polymorphic form

2. Drug Product
Unexpected dissolution properties
Assay values significantly different from theoretical
Unacceptable subjective appearance

These findings may obviously lead to drug substance, or drug product failure, and rejection; but such decisions should not often be taken in isolation of other information and input from other functions. For example, a batch of drug substance with a change in "impurity profile" could be released after appropriate bridging toxicology studies have been performed to qualify the new impurity profile. Changes in dissolution profile could allow release of drug product if supported by convincing in vivo studies.

Such occurrences are not unusual in the development process, and information from different, or out of specification findings, will be used to feedback to the process chemist or formulator to increase the knowledge base to assist with development. Such "problem" findings almost always generate additional analytical work to assist in identification of the source of the problem and may require additional studies by other disciplines, for example toxicology studies or bioequivalence studies in either animals or humans.

Observation of "problem" results always has potential to delay a project, and consequently effective communication is required with other functions in a project team to manage how and when the issue is brought to the team's attention. Too early could be before simple analytical checks have been performed; too late could be viewed as withholding vital information from the team.

C. Interface with Development Process

These questions are commonly asked when analytical managers meet:

How much validation does the company do before phase I, II etc.?
When does the company finalize its quality control and stability methodology?

These questions relate to risk assessment of the development process where greater than 10 compounds per year entering clinical development are required to produce 1 compound per year, as a potential product for marketing (MAA/NDA approvals). Estimates of industry-wide probabilities of success at the end of each phase of development are given in Table 3. With this level of drop out, it is sensible to phase many aspects of development work, and corresponding analytical work should also be phased.

TABLE 3 Probability of Success for a Drug

Phase	Probability of Success to Next Phase (%)
Preclinical	40
I	70
II	50
III	70
Approval	90
Overall	9

1. Drug Substance

Drug substance synthetic route is usually finalized before phase III but could change greatly from preclinical to the end of phase II, which has the potential to change the "impurity profile." It could, of course, be a company policy to retain the same synthetic route from that used to provide drug substance for early preclinical through to commercial manufacture and, therefore, minimize the risk of change of impurity profile. This strategy does conflict however with the research chemist's drive to produce very small quantities of compound by any route, no matter how impractical, and the process chemist's responsibility to:

Produce early preclinical and clinical supplies quickly
Phase resource appropriate to the state of development of the compound
Develop economical and manufacturable processes
Develop safe processes
Develop processes that meet environmental standards.

With the finalization at step 4 of the International Conference on Harmonization (ICH) Impurity Guidelines (12), account should be taken of the principles expressed by this Guideline, although strictly these requirements are not applicable during the development phase. It is usual strategy to ensure that batches with relatively high levels of impurities are used in toxicology studies, but judgment must be used to reduce the risk that large quantities of impurities in drug substance will cause an adverse toxicological finding, which could compromise continued development of the drug. Impurities present at levels above 0.1% need not always be identified early in development, since the actual batch used in toxicology studies may also be used clinically. In practice, impurities at levels greater than, for example, 0.2% are identified from the start of the development process to assist process chemists in their work to optimize synthetic route and process. Consequently, analytical methods need to be adequate to control drug substance for early studies and must be appropriately validated.

ICH requirements (13,14) should be applied to validation of drug substance methods during phase III development. Requirements should be reduced for earlier phases of development, particularly to take account of the following ways methods are operated.

Single laboratory
Few, maybe one, analyst(s)
Specification limits relatively wide
Relatively few batches of drug substance synthesized and used, many of which are used in toxicology studies

2. *Drug Product*

It is inevitable that drug product formulations will change during the development process because of the need to support clinical studies with different objectives, designs, and dose levels. There is much variation between companies for choice of oral dosage form for phase I clinical studies, many informal surveys showing preference for solutions/suspensions, capsules and tablets. Choice depends on company philosophy, history and technology, as much as science.

At phase III, many companies use the final formulation, if at all possible, to minimize risk of bioinequivalence between the phase III and commercial formulations. Throughout the development process within a company, there is usually a strategy to minimize formulation changes, but some change of drug substance/excipient ratio is inevitable to meet the requirements that formulations of different strengths are matched for blinding purposes.

Consequently, analytical methods must be developed and validated to meet the immediate quality control need and associated stability studies. Methods for sales formulations must meet the requirements of ICH validation guidelines (13,14); but for clinical formulations, validation protocols and acceptance criteria should depend on application (e.g., number of analysts, laboratories, skill of analyst, length of studies).

D. Microbiological Testing

Microbiological testing should be considered as another analytical technique that is applied to particular samples. Specialized facilities are required, for example, for (a) sterility testing where an area for sample preparation, complying with class 100 requirements, is desirable; (b) containment of pathogenic organisms, and (c) disposal of samples containing high levels of microorganisms. In addition, specialist microbiological expertise is required to culture and handle microorganisms, to perform sterility testing, and to identify contaminant microorganisms. In this short section, the following major roles of microbiological evaluation are discussed:

Determination of levels of microorganisms (bioburden) in raw materials, including water, particularly those of natural origin, and those destined for use in sterile product manufacture, most especially sterile products that are not terminally sterilized, and in products such as (a) liquid and semisolid products of all types (e.g., oral and topical), (b) suppositories, and (c) topical products applied to unbroken skin

Determination of bioburden of in process samples, for example, solutions before filtration in the manufacture of sterile products

Sterility testing of (a) parenteral products, (b) topical products for application to broken skin, and (c) ophthalmic products

Testing of environmental samples, for example, from air samples and swabs from sterile manufacturing areas, and samples from nonsterile manufacturing areas, particularly those manufacturing liquid products

Testing to support formulation development, taking account of potential use, including challenge testing to support development of optimum preservative levels and minimum preservative levels that could be supported as a specification limit

Microbiological integrity testing of product packaging, both during development of the product and during stability studies

Identification of microorganisms in support of product development, examination of environmental samples, product complaints and returns

Support for validation of terminal sterilization procedures by providing input to protocols, determination of 'D' values of organisms used in studies and completion of testing.

As for all analytical testing, methods should be validated, which requires some minor differences in protocol from conventional chemical methods. For example, methods for sterility testing must be validated to show that they would detect a contaminant organism, if present, which requires studies to confirm that low levels of organisms spiked into a sample solution can be recovered and show growth in the test. In parallel, the operator must operate the test to produce "no growth." This is an extremely important requirement since pharmacopeial monographs and application of cGMPs requires that false-positive results in real samples are investigated fully before any retest is supported. As with chemical testing, limits are derived from pharmacopeial precedent, batch analysis experience, and interaction with regulatory agencies.

Most companies organize their operation such that limulus amebocyte lysate (LAL) testing is performed by the microbiology function. The test itself could be performed by individuals with expertise in various backgrounds, but investigation of positive findings and relationships with the microbiological test results typically require that this testing is performed by microbiologists.

As discussed later (Biologically Derived Molecules) manufacture of biologically derived molecules requires a large degree of input from microbiologists, since many of the operations are performed in aqueous media, at physiological pH values, at temperatures in the range 5°C to 30°C, and in solutions of materials that could easily support growth of microorganisms.

In summary, microbiological testing is an integral part of the Quality Control Unit and should be treated as such, even if organizationally it does not report to an analytical chemistry manager.

E. Pharmacopeial Compliance of Components

It is a territory requirement that excipients in formulations comply with local pharmacopeial monographs (USP, Ph Eur, JP) for commercial products, and it is well known that there are many subtle differences in limit and method between excipient monographs in different pharmacopeias. A monograph harmonization exercise for major excipients is being progressed under the ICH process with the expectation that unified monographs will emerge. Industry associations (PhRMA, EFPIA, and JPMA) are pressing, however, for mutual recognition of monographs (i.e. acceptance of, for example, JP monograph compliance in the United States or Europe) even if a local monograph exists. For clinical trial applications, mutual recognition is accepted, which means that compliance with one particular monograph can be registered and used worldwide for clinical trials. Care must be taken, however, with compliance with regulatory documentation if there is a change of excipient supplier, perhaps resulting from a change of site of manufacture, when a different pharmacopeial standard could be applicable.

F. Limit Setting and Application

The process of establishing limits during the development process is based on several factors such as typical pharmacopeial standards and precedents, and actual analysis of batches submitted to toxicological or other in vivo studies. These limits could tighten as development progresses based on more manufacturing experience and will require extensive evaluation and potential narrowing for NDA/MAA submission. Widening of limits, which would be required to support release of a batch that does not comply with the original limits, requires careful and thorough justification to company management and to regulatory agencies when updates to the IND and CTX are provided.

Limits must also consider the impact of the Barr case judgment (15) to minimize the risk of single, out of specification values, as a result of normal analytical variation, producing results that require an excessive number of laboratory or formal investigations.

Historically, companies have used regulatory, in-house, and/or action limits to assist with judgments for release of drug substance and drug product for clinical use. Definition of these criteria was often not well understood within companies and certainly is different between companies. Current regulatory advice for the United States appears to require simplification of type of limits to (a) limit included in IND and (b) action limit, which would be applied as a means to ensure that the test result complies with specification. This action limit, therefore, would be based on the variability of the method and number of replicates used.

G. Use of Certificates of Analysis and Contract Analysis

For drug substance and drug product manufactured in house, it is usual for analysis to be performed in house also, providing that necessary technology is available. It is possible that facilities and/or expertise to perform a test method is not available in house, for example microbiological analysis, LAL test, and specialist spectroscopy and, therefore, testing must be contracted out.

Data from third parties can be accepted if methods are validated and verified, the company having responsibility to ensure that methods are indeed validated. Usually, verification is performed by a formal inspection of third party facilities, procedures, and methods to ensure that they are acceptable. The European GMP guidelines (1) include a Chapter 7 relating to contract manufacture and analysis.

Active ingredient purchased from a third party and analyzed using a reputable pharmacopeial monograph, or using an agreed specification, could be released for clinical studies without further analysis, if there were assurance that the methods and limits were appropriate and submitted to an IND/CTX or that the company had an approved Drug Master File (DMF) (European or a type II U.S.). A formal inspection should be performed. In these cases, companies must assure themselves that monographs or DMFs contain methods that can evaluate the "impurity profile" of drug substances to allow comparison between batches proposed for clinical use and those used in toxicology studies. It must not be assumed that organic impurity methods in pharmacopeias have appropriate specificity to detect impurities derived from the synthetic route proposed. Some additional validation is required.

Certificates of analysis from excipient suppliers could be accepted without further testing if these suppliers provide evidence of the quality of their work, for example, via documentation (e.g., DMFs) or after inspection by the company's Quality Assurance Unit. Often conventional excipients are used for manufacture of clinical supplies material, which already exist in the company's inventory for manufacture of commercial material and, therefore, could be released for clinical use after analysis by the manufacturing quality control unit.

If third party analysis, or certificate of analysis, is used to provide analytical data for a batch of drug substance, inactive ingredient, or drug product, the company responsible for the clinical trial has final responsibility for release of clinical materials and must take appropriate steps to assure itself that third party data are valid.

Finally, it is often the case that methods have to be brought in house before approval of an NDA/MAA so that they can be applied at least initially or be available if required, to provide the quality control check of material entering a new territory, for example transfer from the United States to Europe, for release for distribution and sale.

VI. DRUG SUBSTANCE, RAW MATERIAL, AND INTERMEDIATE SPECIFICATIONS

An ICH process (Topic Q6A) for small molecules has started work following the ICH Conference in Yokohama, November 1995, which could produce a guideline for setting specifications that applies to new drug substances and new drug products at the MAA/NDA stage. Although applicability to clinical research phase is excluded, these guidelines could be used as guidance for establishing IND/CTX, and in-house specifications. The FDA has issued a draft guideline (16) for comment summarizing specification requirements for NDA/ANDA/INDs.

It is mandatory to provide a drug substance specification in all INDs and CTXs. A typical drug substance specification would include the following tests:

Description
Identification
Sulphated ash/Residue on ignition
Residual solvent(s)
Strength
Related substances
Heavy metals

Additional tests that should be considered are water content, specific catalyst residues, polymorphism, particle size, and stereochemical identity for compounds with a stereogenic center, color and clarity of solution, pH of solution, and residual microorganisms (particularly for use in aseptically filled sterile products).

Limits should be derived from pharmacopeial precedent and analysis of batches used in toxicology studies. In particular, limits for related substances should characterize the material used in toxicology studies, with the additional requirement that batches of drug substance will be released for use in clinical trials, if the impurity profile is the same or better than that of the batches used

in safety studies. Changes in impurity profile should be determined by interpretation of guidelines developed by the ICH process (12). Although discussion is minimal in IND documentation, it is usual to provide batch analysis information to ensure the reviewing chemist that impurity profiles have not changed or are qualified, while either summary batch analysis or a brief statement is provided in a CTX.

Methods should be pharmacopeial, based on pharmacopeial methods, or specially developed with required validation criteria. For the United States, a selective strength method (e.g., chromatographic) is required.

During the early phases of development, specifications for raw materials and intermediates used in drug substance synthesis are being developed, and there is no requirement in Europe to provide information. For the U.S. IND, some specifications or typical analysis could be provided. For solvents, reagents, and other materials used in the manufacturing process, specifications from manufacturing units or suppliers are usually available and are provided in the IND.

In practice, specifications for raw materials and intermediates used in drug substance synthesis are finalized late in the development process, usually at the same time as the definitive NDA/MAA drug substance specification is established since there is direct interrelationship between limits for raw materials, intermediates, and drug substance, particularly related substances limits. These limits could change due to scale up factors, or use of different raw material suppliers.

It is, of course, necessary to analyze raw materials and intermediates throughout drug substance batch manufacture to develop the required databases, for final establishment of specifications. Much more attention is given to routes of synthesis that are to be used commercially. For drug substance, it is normal for limits in the specification to apply both to time of manufature and end of shelf life.

VII. DRUG PRODUCT SPECIFICATION

A drug product specification is also required for an IND/CTX, and fortunately there appears to be mutual recognition of pharmacopeial standards at the clinical stage, which indicates that a company could follow a single pharmacopeial standard. Reference should be made to any output from ICH processes and regulatory guidance, for example, further drafts from the FDA (16).

In the United States, limits given in a specification are expected to apply throughout shelf life, while in Europe there is greater acceptance of separation of limits applied at time of manufacture and at end of shelf life. In CTX documentation, it is usual for a time of manufacture specification to be given, with the view that end of shelf life limits will be derived from ongoing stability

studies performed in parallel to the clinical programme. For the United States, a similar philosophy applies, but care must be taken that the specification given in the IND, for example, dissolution limits, will apply at the end of shelf life.

It is not possible here to define all the tests and limits that could be applied to all dosage forms, but the following general guidelines should be applied as a minimum to a drug product specification:

Description
Identification
Strength
Uniformity of dose to the patient
Measure of drug availability to the patient
Control of degradation
Microbiological control

Obviously tests and limits applied depend on the type of drug product used in clinical studies. Table 4 summarizes typical tests for more common dosage forms that should be included in a phase III IND/CTX. Phase I/II specifications may be adjusted, for example, by omission of degradation product tests since end of shelf life limits may not be determined so early in development.

Dosage forms for inhalation delivery (metered dose inhalers, powders for inhalation) require a different list of tests and limits based on pharmacopeial precedent and could include description, identification, average strength, weight per shot, doses per container, fill weight, particle size distribution, strength per dose, uniformity of dose, propellant composition, degradation products, and preservative level. A harmonized pharmacopeial monograph is being developed (17).

Controlled release formulation specifications must include multipoint (at least three time points) limits to define the dissolution curve at the end of the proposed shelf life.

Additional tests and more extensive application of specification tests could be applied in process during clinical trial manufacture as part of validation of a process and in the protocol applied to examination of manufacture of the so-called Biobatch (that is, the production scale or production-representative scale batch of drug product that is compared in a bioequivalence study to a batch of drug product used in a critical phase III clinical study). For example, more extensive examination of specification tests could be analysis of more time points on the dissolution curve of an intermediate release solid dosage form. Additional tests could be:

Tablet dosage form: dimensions, hardness, disintegration, friability, average weight, uniformity of weight (omit hardness and friability for a capsule). Control of moisture content may be required to ensure good compression or filling properties, or to minimize degradation during processing.

TABLE 4 Tests to Be Included in Phase III IND/CTX

	Tablet/Capsule	Parenteral Solution or Powder for Reconstitution	Multidose Suspension/Emulsion/ Solution	Multidose Cream
Description	x	x	x	x
Identification	x	x	x	x
Strength	x	x	x	x
Uniformity of Content (USP)	x	x		
Degradation products	+	+	+	+
Dissolution (USP)	x			
Water content	+	x[1]		
Particulate matter		x		
pH		x	x	x
Preservative level		+	x	x
Sterility		x		o
Endotoxin		x		
Globule/particle size			+	
Bioburden			x	o
Antioxidant level			+	+
Viscosity				+

x = Include in IND/CTX specification
+ = If appropriate, consider separate time of manufacture and end of shelf life limits in Europe, and assume end of shelf limit in US
o = Include if appropriate to formulation
[1]For lyophilized powder

Parenteral dosage form: withdrawable contents, contents volume
Suspensions/solutions/emulsions: viscosity and dissolution of suspensions, particle, and/or globule size
Creams: particle and/or globule size
Metered dose aerosols of suspensions: morphology

Release of the Biobatch should include compliance with both the registered specification and additional tests and limits used as in process controls, and specified in the Biobatch manufacture and release protocol. Parameters that are a feature of the formulation and not individual batches should not be included in specifications, examples being excipient levels if directly controlled by weighing and GMP, and tonicity.

For controlled release products, establishment of limits should be based initially on in vitro studies of a range of drug products evaluated in vivo using a suitable animal model and/or of products manufactured using a range of control parameters to define the "window of manufacturability." In some territories outside the United States, it is possible to perform in vivo studies in humans, satisfying local ethical considerations but not requiring that in vitro release specification is submitted to a government agency. In effect, these studies are part of development of the controlled release formulation and could be used to establish the specification limit. In the United States, however, it is usual to submit a tentative in vitro release specification in an IND, and this limit will require refinement when results of human in vivo studies become available.

VIII. METHOD DEVELOPMENT AND VALIDATION

A. Method Development

Owing to the wide range of active ingredients that are used during clinical studies, discussion is restricted to generalities. Although pharmacopeial precedent and previous experience with a drug substance or drug product are taken into account, methods for new drug substances should be developed from first principles and using scientific understanding. As a basic strategy, it is highly desirable to have methods finalized for the beginning of phase III, so that definitive regulatory stability studies for drug substance and drug produce are performed using methods to be included in the NDA/MAA without change and for there to be a logical connection between drug substance assay, impurity, and degradation product methods, and drug product assay and degradation product methods. If the same methods can be used for drug substance and drug product, then there is an obvious absence of redundancy of method development, and reviewing chemists are able to see relationships better. Scientifically, it is not necessary to apply methods to drug product to monitor and quantify impurities resulting only from drug substance synthesis. Drug product meth-

ods need to be specific only for degradation products resulting from manufacture and/or storage, as confirmed by the ICH guideline (18), Impurities in New Drug Products. To support this differentiation, good science has to be performed to define potential impurities from synthesis and those resulting from degradation. This differentiation can be achieved by performing Japanese-style formal "forced degradation studies" (Stress Test) to defined protocols on drug substance, with the objective of establishing or confirming (a) the route and rate of degradation, (b) potential degradation products, and (c) methods are stability indicating.

Such formal studies would be performed before finalization of methods for definitive regulatory stability studies. Different companies vary in terms of timing of these studies in the development process, some preferring to delay extensive formal studies until after some critical phase II efficacy decisions have been reached.

Early in development, methods could be used for analyzing synthetic impurities in drug substance, or for controlling raw materials and intermediates used in drug synthesis, which may not be applicable for transfer to a routine manufacturing operation. For example, techniques such as use of high field NMR, HPLC coupled to mass spectrometry (HPLC-MS), GLC-MS or HPLC-NMR could be used, with change to more robust, less expensive technology suitable for routine application (HPLC, GLC, TLC and CE) occurring at the phase II/III interface, when commercial route and process of synthesis are finalized.

Validation of strength and degradation product methods in drug product should be based on knowledge of the drug substance, with additional experience of stress/forced degradation studies used in the development of the product, such as drug/excipient compatibility studies and/or stressed studies on drug product. These studies are designed to determine whether there are additional degradation products in drug product not present in drug substance, and to confirm that the route of degradation is the same in product and substance. Such stress studies could be linked with stability evaluation of clinical formulations where it is usual to include in stability protocols stress testing at elevated temperatures such as 50°C, and in presence of light. These studies are a precursor to formal regulatory stability studies now published in internatinal guidelines (19).

Development of a dissolutuion method should have two distinct components: development of a method that has potential discriminating power based on in vivo or pharmaceutical performance, and validation of the procedure to ensure acceptable accuracy, precision, stability in solution, and linearity. The first objective requires evaluation of biopharmaceutical factors and examination of a range of formulation factors. Different solvents may be used for different strengths of the same drug substance. Methods should be based on those

in current pharmacopeias, a nonpharmacopeial method being allowed only after demonstration that a pharmacopeial method is unacceptable. Extensive evaluation of pharmaceutical processing parameters should be performed on the final phase III/sales formulation to ensure the dissolution method is discriminating. After a discriminating method has been developed, formal analytical validation should be completed, which should confirm accuracy, precision, linearity, and stability in solution. If a separative method is developed as a stability-indicating method, this will normally have sufficient specificity to act as the identity test.

B. Method Validation

Even at the clinical trial stage, methods should be validated broadly in line with ICH Guidelines, Validation of Analytical Procedures (13), the main table from which is reproduced in Table 5. Definition of terms is given in the guideline.

As discussed in PHILOSOPHY OF QUALITY CONTROL FOR WORLDWIDE CLINICAL SUPPLY, the extent of validation could vary depending on the stage of development of drug substance and drug product, and need not follow exactly the ICH guideline, Validation of Analytical Procedures: Methodology (14), which is intended for application to analytical procedures included in MAA/NDA submissions. For example, number of replicates in a precision study could be fewer, accuracy criteria could be wider, and limits of quantitation could be higher for methods applied early in development.

IX. DETERMINATION OF EXPIRY DATE

Stability testing is discussed in Chapter 11. Expiry dates for clinical supplies could depend on any parameter that has the potential to change. One of the challenges for the group that establishes expiry dates, normally the quality control unit, is to determine the proposed end of shelf life limit for that parameter.

For degradation products, knowledge of the rate of degradation, and identification of potential degradation products of drug substances is an essential prerequisite to development of suitable methods for both drug substance and drug product. Additionally, this information should be used in discussions with toxicology colleagues concerning definition of a limit for degradation products, using the principles given in Impurities in New Drug Products ICH guideline (18). The need, or otherwise, for additional safety studies depends on whether the degradation products are also present in drug substance as impurities, or whether they are metabolites, in both cases degradation products being relatively easily qualified. For other cases, knowledge of the structure helps in the discussion with the toxicologist. In the final case, it may be necessary to peform

TABLE 5 ICH Validation Guidelines

Type of Analytical Procedure	Identification	Impurities Purity Test		Assay Content/Potency/Dissolution
Characteristics		quantitat.	limit	measurement only
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Intermediate precision	-	+(3)	-	+(3)
Reproducibility	-	-(1)	-	-(1)
Specificity	+	+	+	+(2)
Detection limit	-	+	+	-
Quantitation limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

-signifies that this parameter is not normally evaluated.
+signifies that this parameter is normally evaluated.
(1)May be needed in some cases.
(2)May not be needed in some cases.
(3)In cases where reproducibility has been performed, intermediate precision is not needed.

a safety study on degraded material to help define the limit for a degradation product.

For other parameters that could change during storage, scientific judgments must be made regarding changes in level, particularly if these changes occur during storage at accelerated conditions. For example, change in dissolution profile during storage at accelerated temperature may not occur at 25°C. Change in dissolution profile at the defined label conditions requires reference to biopharmaceutical studies, and judgments must be made about the significance of the change.

For most parameters, application of the Arrhenius equation should be considered:

$$k = Ae - \frac{Ea}{RT}$$

where k = reaction rate, A = Arrhenius constant, Ea = activation energy, R = gas constant, and T = absolute temperature. Empirical derivations of this equation are helpful; for example, a rise of 10°C doubles the rate of reaction. Of particular value is the observation of no change after storage at accelerated conditions, when projection of expiry date can be made with good assurance.

In the United States, it is not necessary to include expiry date on the label of clinical supplies, although many companies do. Assurance of quality in this case is provided by a parallel supporting documentation system, by knowledge of location and control of clinical supplies, by continuing prompt evaluation of stability samples, and in the worst case, by availability of an effective recall system.

In many territories, it is a legal requirement to include the expiry date on the label of clinical supplies and for those territories, scientific extrapolations of stability data are required to produce projected expiry dates. It is impractical to continue a stability study to completion *before* commencing a clinical study. Similar criteria are applied to stability studies of drug substance, but with the aim of projecting a retest date.

X. DOCUMENTATION

The key documents for scientific, regulatory, and compliance requirements are (a) laboratory notebook, (b) test methods and limits (specifications), (c) regulatory application—IND, CTX, and (d) in-house dossier.

Documentation of laboratory controls and operations must be performed in compliance with sections 211.160 General Requirements and 211.194, Laboratory Records of the Code of Federal Regulations (CFR) (2), and Chapters 4 and 6.7 of the European Rules Governing Medicinal Products in Good Manu-

faturing Practice (1). Little further explanation is required. Laboratory notebooks should preferably be bound, but use of prenumbered pages issued by a secure system is acceptable. Data must be entered directly into notebooks, or into validated computer systems, and the initials or signature of the person who performs the test must be associated with these data. A second person must review records for accuracy, completeness, and compliance with established standards. Raw data, in the form of handwritten information in notebooks, chromatograms, or electronic information must be defined, authenticated, and archived securely.

Written specifications must be available, neatly presented, usually typed, and approved. During the early phases of development, procedures must exist to deal with changing methods to ensure that the laboratory remains in compliance with in-house and regulatory documentation.

Compliance with limits provided in regulatory applications is a European and U.S. requirement, but compliance with registered methods is only a U.S. requirement; the European CTX does not require detailed description of analytical methods. To facilitate assembly of regulatory documentation, it is common to submit in phase III INDs details of the methods as written for the laboratory rather than rewriting the method specifically for the IND. Change of method is then facilitated by presenting a new or revised method as part of an IND update before clinical supplies are released using that method.

The structure of key regulatory documentation is very different, the phase III IND being a more comprehensive document of data. Indeed the CTX, as a summary document, can be derived from the IND and there is some skill in ensuring that statements and judgements are made by the author and supported by examples of data, without providing large quantities and tables of data.

As given in the CFRs, all laboratory operations and procedures must be written and approved, and contain details of calibration. Additionally, the quality control unit has responsibility for review and approval of written procedures for production and process control of drug product.

The CFRs require that records should be retained for at least 1 year after expiration of a batch. Since many companies do not formally assign expiry dates to clinical supplies and when they do, the expiry date could come many years before an MAA/NDA is approved and PAI completed, production and control records should be retained for at least 2 years after termination of discontinuance of the relevant IND, or at least 2 years after the date of approval of the relevant NDA (5).

XI. APPROVAL PROCESSES

Organizations and reporting relationships vary greatly among companies, but if Quality Assurance Units are considered part of the quality control function

as defined by GMP regulations, the flow chart (Fig. 2) represents stages in the manufacture and packaging of drug product from drug substance, where the quality control function has responsibility for approval. As discussed in Organization, Personnel, and Training, many companies have a separate Quality Assurance Unit that performs an independent review of specifications, master batch production, and packaging records. It reviews actual batch and packaging records for relevant steps in the manufacturing and packaging process and associated analytical data in order to give a release/reject recommendation. In addition, within the analytical part of the quality control function, the analyst must review and sign his or her own work, which must be checked by a second person, and all data reviewed and approved, usually by a more senior person who would make the recommendation for release or rejection.

XII. SAMPLING

Sampling has always been a vital feature of analytical testing since it is the first connection between an analytical value representing the batch and the batch itself, and hence must be random. Sampling has become even more important since the Barr verdict (15) in the United States. Interpretation from this case would not allow routine resampling as part of a process to determine if a batch could be released following observation of a single or multiple out of specification results. Resampling could only be justified as part of a full protocol-driven investigation, which is approved by a more senior person.

GMP regulations require that sampling is performed in accordance with approved written procedures. Owing to the wide variation of active ingredients, components, and drug products used in clinical trials, and with an equally wide range of processes and scales of manufacture, a standard procedure cannot be given. Great attention must be given to premixing of material if this is possible, or when taking samples either during manufacture (e.g., tabletting or encapsulation) or when present in a large bulk container.

In addition to the mechanism and location of sampling, attention must be given to size of sample. For example, the Barr case judgment has given some guidance to size of sample (three times a drug product unit dose) that should be taken from the granulation stage to determine blend content uniformity.

The most useful reference to provide guidance on sampling in the United States is the military standard (20,21). Owing to the range of substances and products, interpretation to produce a particular company's sampling procedures is required.

Companies must also take account of specific requirements (22) in terms of location, size, and security for samples of drug product used in key regulatory bioequivalence studies. In this case, the sample size must be large enough to allow five full retests.

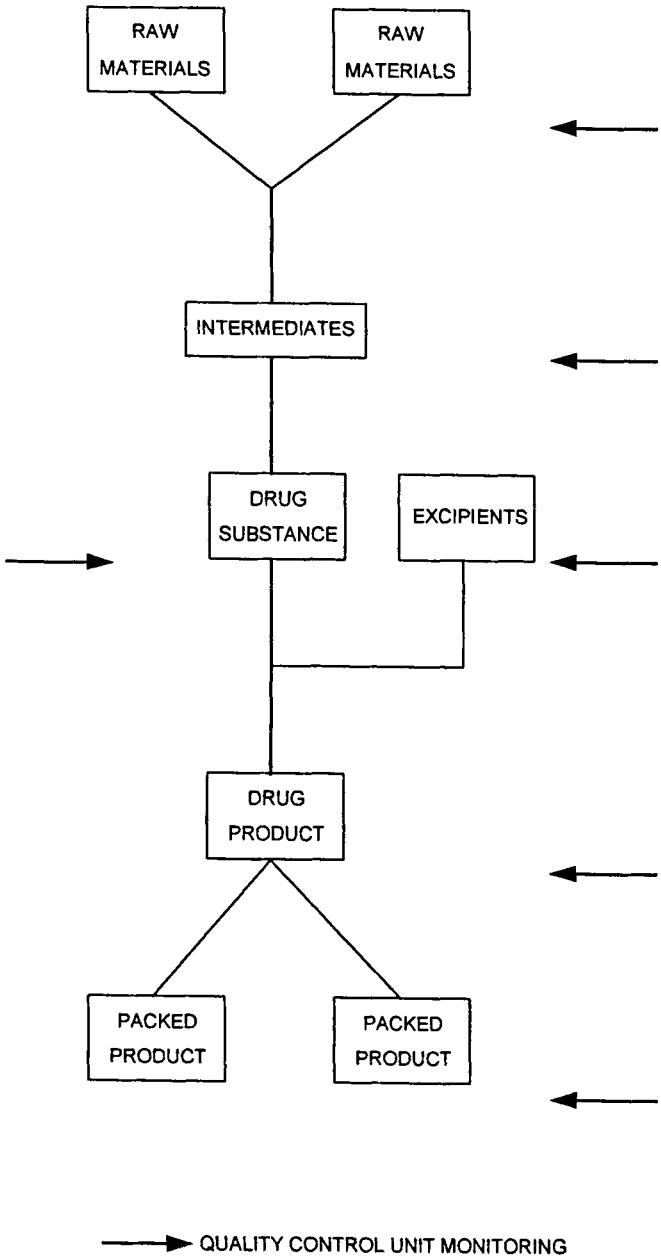

FIG. 2. Quality Control Unit responsibilities.

In addition to testing of final products from a process, great additional assurance of quality is achieved by more detailed in-process sampling and testing than would occur with routine batch manufacture of drug product. Use of this level of additional sampling and testing should be documented in the form of batch record or protocol and could be considered as part of concurrent validation of drug product manufacture for clinical trials, when it is very difficult, owing to lack of availability of drug substance to perform the usual repeat of manufacture of three batches to a predefined protocol.

XIII. SUPPORT FOR CLEANING

Cleaning between batches of drug product and during drug substance synthesis requires control and is an issue receiving more attention, as companies ensure their procedures meet the spirit of the FDA cleaning guidelines (23). There is some variation between companies in terms of derivation and calculation of limits for residual material after cleaning, but most procedures do require analysis of swabs. Methods applied to swabs must be selective for the agent concerned, which could include cleaning agents (e.g., detergents), and estimated recoveries must be derived. Analysis of a subsquent placebo batch, or the subsequent batch itself, for presence of drug substance from the previouis batch is discouraged.

XIV. BIOLOGICALLY DERIVED MOLECULES

Most of the comments in the previous sections have been based on synthesis of a small molecule drug substance and manufacture of the corresponding drug product. With the expansion of the number and type of biologically derived molecules in development, many of the same principles and procedures can be applied. Since biologically derived molecules may not be pure, single molecular entities and, even if pure, are very diffiult to characterize in terms of molecular structure, particularly tertiary structure, it is not possible with current analytical technology to assign identity and purity to the same level of confidence as can be assigned to a small molecule. As a result, much greater attention must be given to number, frequency, and type of in-process tests applied during manufacture of large molecules.

In parallel with work on small molecules, an ICH process (Topic Q6B) has commenced work to produce a guideline for setting a specification for a biologically derived product. Before any manufacture of a biological product, some quality control at a molecular level is required for recombinant cell lines. It is imperative to establish the geneology of the host strain and to ensure selection and stability of transformed cells. Master and working cell banks must be established and validated to ensure the integrity of any cloned coding sequences.

Since these biological processes are performed in aqueous media, many of which provide excellent growth media for microorganisms, greater attention must be paid to microbiological quality of starting materials, equipment, and environment, when in many cases, full aseptic processing is required. As an adjunct to microbiological evaluation, endotoxin levels must also be monitored carefully. Presence of microorganisms not only could provide unacceptable endotoxin levels and potentially nonsterile injectable products, it could also disrupt or compromise biological processes.

Before clinical trial manufacture of a biological product, a full review of the process should be performed by a multidisciplinary team, which should include representatives from the quality control unit to determine the number, frequency, and type of in-process tests applied.

Characterization of biological molecules is a rapidly evolving science. Nonetheless, identity, purity, and apparent molecular weight are often determined by a range of electrophoretic techniques, reverse phase, ion exchange, and gel permeation chromatography. Specialized spectroscopic techniques are applied, e.g., soft ionisation mass spectrometry to determine molecular weight and monomer/oligomer sequences and high field NMR to determine monomer content, monomer ratios, and primary, secondary and tertiary structures. In addition, more conventional amino acid and nucleic acid sequencing methods are applied. Consistency of tertiary structure can be confirmed by application of optical rotatory dispersion (ORD) and circular dichroism (CD) techniques.

Biological activity should be determined in vitro (e.g., antigen binding and enzymatic lysis), by a technique that has some relationship to in vivo performance, with careful statistical design of replication required to minimize variability of the final result. A statistician should be employed in design of replication and calibration of such in vitro methods. In some cases, biological activity can be determined only by an in vivo test, and careful design is required to minimize variability.

Depending on the type of large molecule and the process by which it is produced, tests and limits could be applied on a batch basis in addition to those applied to small molecules, for example:

Residual DNA
Immunogenic potential
Special in vivo safety tests
Absence of viruses

In common with small molecules, consideration should be given to apply tests and limits to confirm acceptably low levels of any reagents used either in biological synthesis or in isolation and purification (e.g. extractives from affinity columns).

XV. EXCIPIENTS

As discussed in Philosophy of Quality Control for Worldwide Clinical Supply, mutual recognition of pharmacopeial monographs for excipients is accepted at the clinical trial stage; therefore, compliance with a single pharmacopeia can be used worldwide. Care must be taken to ensure that new products use excipients that have a current pharmacopeial monograph. Choice of an excipient that does not have a monograph requires that the supplier provide information to ensure that the material is safe for human consumption. This assurance could take the form of recognition as a food additive, included in the Generally Recognized As Safe (GRAS) list, or could be provided by supporting safety information. Without this assurance, it must be assumed that the material is new and characterization, safety, and stability studies will be required, which are equivalent to those for a new drug substance.

If coloring agents are used, they must comply with local requirements, which are Food, Drug and Cosmetic standards in the United States; in Europe, quality standards given as E numbers apply. It can be difficult for the same coloring material to meet both these criteria, with the exception of iron oxides. Hence it is perhaps advisable to omit coloring agents at the clinical stage. Omission of coloring agent, however, may compromise a strategy that requires phase III and commercial formulations to be identical. Water used in later stages of drug substance synthesis and in drug product manufacture must comply with a recognized pharmacopeial monograph, with additional tests and limit for microbiological levels applied. Very strict microbiological limits and storage time (within a few hours) are required for Water for Injection, which is used in manufacture of sterile products.

XVI. COMPARATORS

The extent of quality control work applied to comparators used in a company's clinical program depends greatly on the approach taken to provide a comparator, which often could be available generically. The following options are available:

1. Use as received
2. Make very minor modification, for example removal of print
3. Make minor modification, for example filling a tablet into a capsule shell
4. Make major modification, for example, regrinding a tablet, recompressing or filling of ground tablet powder into a capsule shell
5. Develop comparator product
6. Obtain granule from another company and compress/fill
7. Purchase finished dosage form from another company or from open market.

Issues that need to be considered in each case are the following:

1. To minimize testing, attempts should be made to obtain expiry date of the batch, either from the label or from the manufacturer. Repackaging from commercial into a clinical pack may require stability testing, which would require knowledge of methods and availability of reference material.
2. The issues in this case are similar to those in (1) with the additional requirement to assess the impact of the "very minor modification" on quality and expiry date. As a minimum, it is often necessary to apply an in vitro comparison of modified and original products.
3. The issues are similar to those in (1) with the additional requirement to examine in vitro release carefully, to compare with original dosage form. It would be normal to perform a stability study to confirm no change in in vitro release for the period of the study. It should be hoped that the dissolution method is available in a pharmacopeia; if not, a method must be developed.
4. Major modification will require release testing, including at least in vitro comparison with the original product. Depending on biopharmaceutical properties of the drug, in vivo comparison may be required and be desirable to ensure that the resulting clinical study is not questioned. Stability studies will also be required.

   Methods and reference material could be available from a pharmacopeia or the originating company. Agreements between some companies would allow provision of methods usually, but not always, after provision of clinical protocols and definitely after agreement of no liability on the originating company. Finalization of legal agreements between companies could be protracted exercises.

   Development of stability methods is resource- and time-consuming, and essentially is a project in itself. Firstly, a thorough review of the literature is required to establish degradation pathways and methods that either have to be developed or changed for application to a particular modified product. Reference material could be obtained from the originating company, a generic drug substance supplier, extraction and purification of drug substance from drug product, or finally by contract synthesis.

   When manipulating an existing marketed controlled release dosage form for clinical studies, there are great risks that the resulting product will have different in vivo performance. Hence other strategies of drug development should be considered to obviate this requirement, for example, arranging supply of product from the originator, or from a generic competitor, or arranging the design of the clinical studies to provide for pharmacokinetic comparison rather than blinded comparisons using clinical end points.

5. Development of a product almost always requires development of impurity methods, for example, for degradation products and a method to monitor in vitro release, if a pharmacopeial method is not available, and generation of stability data. Similar to (4), great consideration shold be given to a bioequivalence study between the developed product and brand leader. There are risks in this strategy that the developed product could be bioinequivalent when tested. It is highly desirable for a company to have knowledge of the in vivo performance of comparators included in its clinical studies.
6. Purchase of granule from another company should also be associated with provision of methods that require application for release and drug product stability studies. It is not unusual to agree to share data.
7. Purchase of dosage form from another company should be arranged, if possible, so that an expiry date is also provided.

XVII. REFERENCE MATERIALS

In the early stages of development, the most pure batch is sometimes characterized thoroughly for purity, using a multiplicity of techniques that produce data that can be compared, a purity value assigned, and this batch used as reference material. Companies often have higher standards of purity criteria (e.g., >99.5%) for a reference material, compared with normal standards of material released for preclinical studies and early human clinical studies (e.g. >98%). If these standards are not met by an initial batch, then recrystallization would be performed until satisfactory reference material purity is achieved. Reference material used to support release of drug products in critical phase III studies is normally recrystallized, even if purity criteria were already achieved. Once a reference material has been defined, it must be carefully stored, for example, at low temperatures such as 5°C or -20°C, which does require that equilibration with room temperature is performed before subdispensing laboratory working standards. The primary reference material stored at low temperature must be given a retest date and appropriately retested, and corresponding working standards, which could be left at room temperature for short periods, should also be given an expiry date, beyond which it should not be used without retesting.

Early in development, a few grams or tens of grams will be sufficient for a reference material batch, but later in development hundreds of grams will be required, with the aim that quantities could support early sales manufacture. Different purity standards could be applied to reference materials used for different purposes. For example, greater than 99.5% is often required for purity of a reference material used for drug substance or drug product assay, while a reference material for an impurity used in a related substance test could be

95% pure. Reference materials will also probably be required for raw materials and intermediates used in chemical synthesis; the purity criteria depend on the application.

XVIII. PACKAGING MATERIALS

Quality control applied to packaging components is usually relatively little at the clinical trial stage; great emphasis is placed on careful examination of suppliers' certificate of analysis, subjective examination of samples of materials, and possibly some dimensional measurements. Many companies standardize the packaging components used for clinical supplies to restrict inventories, simplify packaging procedures, standardize presentation of clinical supplies, and minimize stability testing requirements.

It is difficult to source the same specification packaging components in different countries; therefore, companies must accept minor differences in packaging components (materials or dimensions) between sites of clinical trial supply packaging if in they are different countries or standardize them by supplying transnationally from a single packaging supplier.

Unlike Europe, the United States IND requires details of packaging materials such as names of materials used in manufacture, dimensions, and reference to a packaging manufacturer's DMF. In a European CTX, only brief reference to packaging components, for example "high density polythene bottle," is required.

If a clinical trial is being performed in several territories and is being packaged at different sites that could be using different but equivalent packaging components, an efficient strategy could be to perform stability studies in the U.S. packaging components and show that the European packaging components are equivalent. This reduces the burden of stability testing applied to clinical materials packaged into European components.

Packaging components should be treated as any other material used in manufacture of clinical supplies, with retained samples taken, formal documented release procedures applied, and testing performed where appropriate.

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11

Stability of Drugs and Drug Products in Clinical Packaging

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Packaging is an important (sometimes the most important) component in the fate of a drug in a dosage form. Improper packaging and viscicitudal storage may cause larger than expected losses in strength; For this reason, the Food and Drug Administration (FDA) has suggested the performance of stress tests dealing with exposure to both accelerated moisture and temperatures.

I. STABILITY STORAGE CONDITIONS OF CLINICAL TRIAL SAMPLES

The second component, the viscicitudal storage, has been addressed by the FDA and USP has addressed in the enactment of the Prescription Drugs Manufacturing Act (PDMA), which states that any condition during the distribution chain of a product must match those in USP xvii. These require a temperature only sporadically exceeding 25°C (and never exceeding 30°C or falling below 15°C) and a relative humidity requirement of 40 to 60%.

The PDMA requirements are to be monitored by state enforcement inspectors. How effective they will be remains to be seen. After all, the speed limit between Madison and Milwaukee, Wisconsin, is 65 mph, but that low speed limit is only adhered to if a state police car is around. Similarly, it is doubtful that within-limit storage in pharmacies and warehouses can be ascertained.

Even worse is the situation in clinical trials. For instance, in outpatient situations, the dosage form encounters a completely capricious environment, ranging from storage in warm hallways and green-house effects in physician's cars to storage in refrigerators when such requirements are not called for.

The monitoring of clinical trial stability, therefore, requires even more diligence than that of regular production. Whatever the new guidelines will require with regard to temperature and humidity should be followed when clinical trials samples are tested.

II. GENERAL POLICY FOR STABILITY TESTING OF CLINICAL TRIAL SAMPLES

For manufactured products, it is customary to sample and test the first three batches produced and then test one batch (or 2% of produced batches) in subsequent years. This is referred to as a skip-lot sampling plan.

The general plans used by companies for stability studies of clinical materials differ greatly. Many companies will test the first three clinical batches, as if they were a manufactured product, and then test yearly thereafter. In this scheme, the largest and smallest of each container-closure should be tested, but most clinical testing is either in (a) one particular bottle or (b) in blister packs, so that the multitude of package testing is less than in a manufacturing situa-

tion. It can be more, however, depending on whether one considers one "card" a special package or a general package. If, for instance, one card is made with two rows of placebo and two rows of active drug (e.g., a 4 × 10 blister), and if in another case it consists of one row of placebo and three rows of active drug, and the blister and packaging material were the same, then it would be difficult to visualize that the stability of the drug substance should be different in package A and package B. However, pedantic adherence to the law might make an inspector or reviewer deem the two different, and could opt to reject (483) at the time of the NDA preinspection.

Other companies take the position that all clinical batches should be tested to ensure that (under the test condition) the batch was stable as long as it was tested in the clinic. Extra diligence is probably the by-word in clinical stability. The lack of control of the distribution environment is of particular concern and the more on-site testing is done, the more one may be assured that the product/package is robust.

There are three essential product types: (1) liquid products, (2) solid dosage forms, and (3) solid/air type products (aerosols). The latter are a specialized type product that will not be dealt with specifically. As with the two other categories, the type of testing carried out (hardness, viscosity, pressure drop) will not be discussed, since FDA Stability Guideline or texts on the subject give detailed descriptions of them. This chapter discusses the phenomena important in the attaining (or loss) of stability.

III. STABILITY OF LIQUID DOSAGE FORM CLINICAL TRIAL SAMPLES

The liquid dosage forms can be broadly classified as: aqueous solutions, suspensions, and emulsions (e.g., solutions for injection, suspensions such as gantanol, emulsions such as Aristocort cream) and nonaqueous solutions and suspensions (e.g., ointments in petrolatum such as aureomycin cream, soft shell capsules, aerosol concentrates). Packaging materials can be glass or plastic (mostly high density PE (polyethylene, bottles), PVC (polyvinyl chloride), or PVC/PVDC (polyvinyldichloride, blisters)).

A. Liquids in Glass

Glass is nonpermeable to moisture and to oxygen, so that any mass exchange with environment must take place through the closure system. Glass, however, is not unreactive (as witnessed by the fact that USP describes more than one type of glass). Particularly in injectables, visual manifestations of such interactions can occur. These are usually due to alkaline attack on the glass, or by preparations containing fluoride. The special nature of such interaction is product dependent.

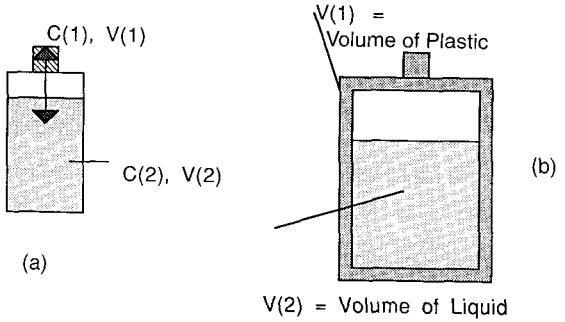

FIG. 1. (a) Schematic of vial and (b) plastic bottle with liquid.

General, however, is interaction with the closure. Consider a vial, such as shown in Fig. 1a.

This type of system is considered a two-phase system, considering the plug (in this case) one phase (denoted "1"), and the solution the other phase (denoted "2"). In such systems, the law of partition requires that:

$$C_1 = KC_2 \tag{1}$$

where K is the partition coefficient, and C_2 and C_1 are the respective concentrations. When the product is first made, C_1 is zero and C_2 is the initial concentration of drug in the dosage form. It will be assumed in the example to follow that the drug is chemically stable, and that the volume of the plug is V_1 and that of the solution is V_2. The original amount of drug in solution is M_0 grams, and after equilibrium it is M* grams so that $M_0 - M^*$ grams have been transferred to the plug. Hence, dividing these two amounts by the respective volumes:

$$M^*/V_1 = K(M_0 - M^*)/V_2 \tag{2}$$

Only K is unknown and once M* (or rather $C^* = M^*/V_2$) is determined then K may be found. A good example of this is the work by Mendenhall (Fig. 2).

This type of behavior is first order (actually equilibrium kinetics), and if the concentration, C, is transformed in the following fashion:

$$\ln[C - C^*] = -kt + \ln[C_0 - C^*] \tag{3}$$

then a straight line is obtained (Fig. 3). k is here the sum of the absorption and desorption rate constants as in conventional equilibrium kinetics.

In general, one does not consider the possibility of moisture permeation or loss from a glass container, but special cases have been reported (ampoules,

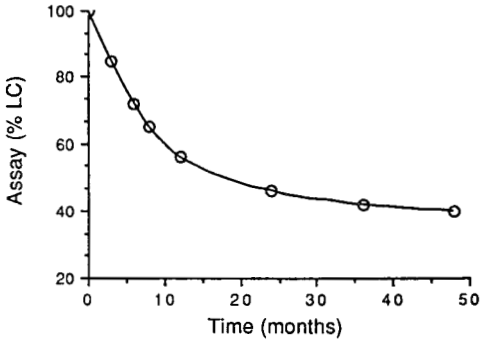

FIG. 2. Data benzyl alcohol disappearance from a parenteral solution into a butyl rubber closure (1).

for instance, by McVean et al., (2)), where cracks formed in ampoules, and the mechanism of the mass transport in vials has been discussed by Morton (3) and Morton and Lordi (4,5).

B. Liquids and Semisolids in Plastics

Exactly the same consideration holds for a liquid in a plastic bottle, where here V_1 is the volume of plastic (i.e., not of the container, but the actual volume occupied by the polymer material).

Leaching and absorption are opposite reactions that can take place between plastics and drug product. It is not confined to aqueous solutions. For instance Tigan (an antiemetic once marketed by Roche), when formulated into a suppository, requires the addition of benzocaine to abate irritation. To avoid interaction between foil wrap and suppository, the wrap was coated with poly-

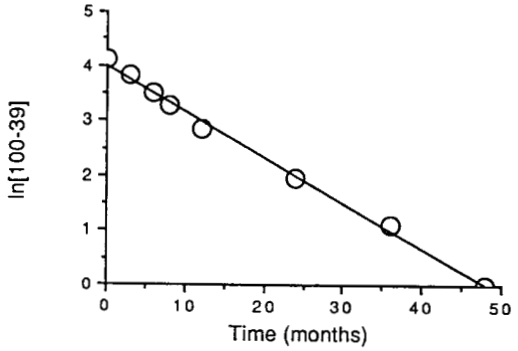

FIG. 3. Data from Fig. 2 linearized by Eq. 3. The least squares fit is ln[100-39] = 4 - 0.0833 t with a correlation coefficient of R = 0.999

ethylene. The result was that 40% of the benzocaine migrated into the coating within 3 months.

The relative volumes are important, but so are the relative solubilities. Eq. 1 holds when both phases are saturated, so that one may write:

$$K = S_1/S_2 \quad (4)$$

where S is solubility. If the solubility, S_2, in the "packaging-phase" is much higher than in the product phase, S_1, then K is large, so that the eventual equilibrium level is low.

The same considerations hold for soft shell capsules. If an oil fill is used, this will constitute an oleaginous "product-phase #1" and the gelatin will be aqueous "product-phase #2", aqueous because it always contains some water. This type of transfer is usually negligible.

Another type, however, is when the gelatin contains polyethylene glycol (PEG) as fill. Glycerin from the shell is soluble in PEG; hence it is customary to formulate the gelatin with an equilibrium amount of PEG and the fill with an equilibrium amount of glycerin. In this case, there is also a migration of water from the shell into the fill because water is miscible (in all proportions) with PEG. This can have biopharmaceutical effects, because if the drug substance in the fill is water insoluble, it may precipitate out, giving rise to lower blood levels.

C. Semisolids in Clinical Trials: Interaction with the Container

Here, as in the case of aerosols, the use of metal in the container can occur, and this gives rise to the possibility of interaction of product with container in a chemical sense. In the case of aerosols, for instance, the use of halogenated hydrocarbons, even when small amounts of moisture are present, may cause the production of hydrochloric acid, which will attack the metal container. Even if a container is coated, will there be this possibility because of flaws in the coating. The use of the coating can give rise to migration of drug substance into the coat.

IV. SOLID DOSAGE FORMS IN STABILITY TESTING OF CLINICAL TRIAL SAMPLES

In the case of solids, there is only rarely a chance for direct exchange between container and dosage form. However, such cases do exist.

A. Interaction Between Plastic and Dosage Form

Plastics contain monomers and plasticizers (and initiators and catalysts) in small

amounts. These should be considered as being dissolved in the plastic. There is the potential for transfer of these substances into the solid dosage form at contact points.

Here, again, the solid dosage form should be considered a solid containing water in some type of adsorbed form (i.e., as a bulk moisture phase), and the contact point provides a locale for exchange of solutes in and out of this bulk phase.

The reason that such interactions are rare (e.g., in bottles) is that the contact areas (A) between dosage form and plastic are small. If the area is small, then the rate of interchange is given by Fick's first law (6):

$$dM/dt = -ADdC/dt \quad (5)$$

where M is amount transferred (in or out) of the bulk moisture layer, D is diffusion coefficient, C is concentration in the bulk moisture layer, and t is time. If the right hand side is a small number (because A is small), then the increase in concentration in the dosage form (dC/dt) is also small (Fig. 4B).

In a bottle, the pressure on the tablets is small, so that the contact area is small, and the exchange is small. Furthermore the bottle is rigid and can in no way "hug" the dosage form. In a storage bag—usually a large, heavy gauge, plastic bag,—the volume of the package phase is large, and there is substantial pressure on the tablets. The bag (Fig. 4A), furthermore, is flexible,* so that the contact area is large; hence, in such cases, transfer of (in particular) antioxidants from the plastic into the dosage form can be sufficiently large to cause unexpected decomposition of the dosage form. The most important aspect of drug instability in packages is, however, the result of moisture.

B. Effect of Moisture on the Stability of Solid Dosage Forms

The effect of relative humidity on pharmaceutical properties is probably the most important cause of both physical and chemical instability of both drug substance and drug product.

Most drug products decompose by way of a zero order reaction scheme:

$$M = M_0 - k_0t \quad (6)$$

where M is drug substance present in the dosage form at time t, and M_0 is the initial amount of drug present. k_0 is the pseudo zero-order rate constant (7). In other words, if the percent label claim (M) is plotted as a function of time (t), a straight line results. The slope of this line is the pseudo zero-order rate constant, k_0.

The value of this is a function of the residual moisture in the tablet, (X mg/g of tablet). It can be shown (8) that below a certain moisture level, A

*The author is indebted to Dr. Donna Gilbert for technical assistance on this point.

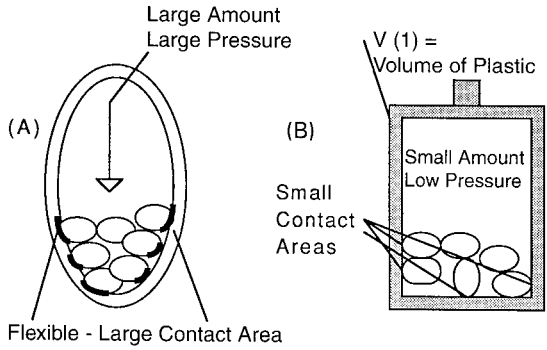

FIG. 4. (A) Drug dosage form in a Bulk Plastic Bag and (B) in a plastic bottle.

mg/g of tablet, the moisture is of no consequence (and this is denoted the bound moisture), but once A is superseded, the rate constant starts increasing linearly (Fig. 5).

If a drug product with a critical moisture content of $a\%$, originally is fairly dry (e.g., b % moisture) and is stored in a plastic package that allows a moisture permeation of m mg per day, and if the bottle contains 100 tablets @ Q gram, then the moisture amount in the bottle to start with is 100Qb/100 = Qb grams. The allowable amount of moisture is 100Qa/100 = Qa grams, so that Q(a–b) grams may be picked up. This will happen in Q(a–b)/m days. This argument is approximate, since the moisture penetration is not linear (i.e., not a given amount per day).

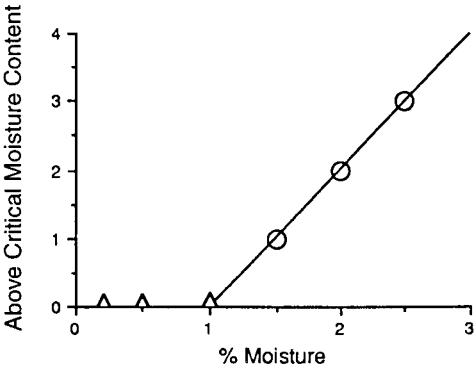

FIG. 5. Stability as a function of amount of moisture in a tablet or capsules. The data are idealized, and the equation for the line through the data points above the critical moisture content (circles) is: Y = -2 + 2 x, i.e. the critical moisture content is when Y = 0, i.e. x = 1%.

V. WATER ACTIVITY AND HOW TO ESTABLISH CONSTANT RH

Before discussing the effect of the environment on the packaged drug product for clinical trial, a short discussion of the properties of water and water vapor are in order, and a few definitions are presented first.

Water activity, *a*, is the ratio of the vapor pressure of a solution, P_{aq}, and the vapor pressure of pure water, P_{H20}:

$$a = P_{aq}/P_{H20}, \tag{7}$$

The *relative humidity*, RH, is defined as 100 times this number and, hence, is a percentage figure:

$$RH = 100\ a \tag{8}$$

Constant relative humidities are accomplished by the means of saturated salt solutions. The well-known law of vapor pressure depression states that for an ideal solution:

$$(1-X) = P_{aq}/P_{H20} \tag{9}$$

where X is molefraction of solid. It is noted that for electrolytes, X is based on the number of atomic particles, so that for a 1:1 electrolyte, the equivalent weight is the molecular weight divided by 2, for a 1:2 electrolyte divided by 3 and so on.

The vapor pressure over a solution, according to Eq. 9, will decrease up until the point where the solution is saturated, X_s, and if solid is added beyond that point, the added particles will not dissolve, and the water vapor pressure will stay constant. Hence such a "suspension" will have a constant vapor pressure, which for a saturated solution is given by:

$$(1-X_s) = P_{aqs}/P_{H20} \tag{10}$$

Vapor pressures of different "salt-solutions" are listed in most handbooks. By placing solution and an excess of solid in the bottom of a desiccator, the RH of the atmosphere in it will be that governed by the saturated solution of the compound.

VI. HYGROSCOPICITY OF POWDERS

One of the components leading to the rate with which a critical moisture content is reached is the hygroscopicity of the dosage form.

A. Isotherms and Moisture Uptake Rates

Powders have isotherms, mostly of the BET-type. If a drug substance (e.g., a very hygroscopic substance such as a lithium salt) is placed on a Petri disk in

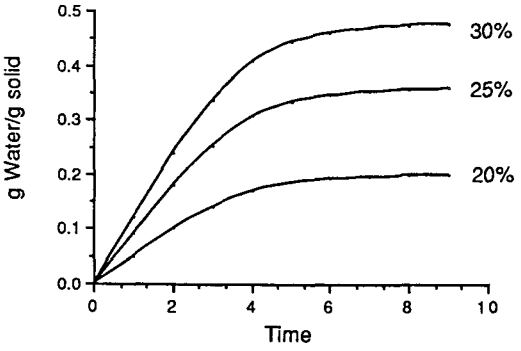

FIG. 6. Moisture uptake rates of a substance at different relative humidities.

an atmosphere of a given humidity (RH-value) and weighed as a function of time then, in most cases, the weight increase is due to moisture uptake. Hence the moisture uptake can be monitored as a function of time. Such an experiment can be carried out in a desiccator or in a vacuum balance (10), using concentrated salt solutions to ascertain the relative humidity.

If this is carried out at several different relative humidities, moisture uptake curves will result (Fig. 6).

The initial parts of these curves are linear, and the moisture uptake rates, y, (Fig. 7) can be deduced from them, although it is possible to treat the entire curve. It is seen from the graph that the equation for the line is:

$$\begin{aligned} y &= -0.883 + 0.07RH \qquad (RH > 12.6\%) \\ y &= 0 \qquad (0 < RH \leq 12.6\%) \end{aligned} \tag{11}$$

The domain is obtained from the fact that the high RH part of the curve intercepts at $0.883/0.07 = 12.6\%$. The latter part of the statement is, strictly speak-

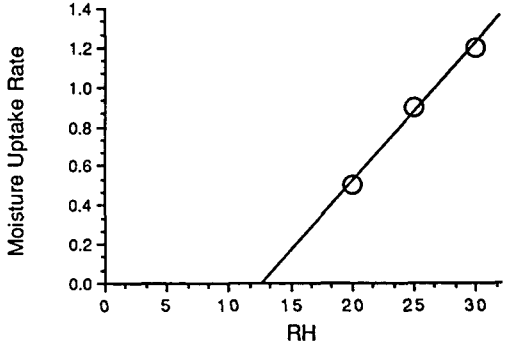

FIG. 7. Moisture uptake rate data. The equation for the line is: $y = -0.883 + 0.07x$.

ing, not correct, because below 12.6% there is still water adsorption, but by way of a BET isotherm.

The division point between the two domains (i.e., 12.6%) is the water vapor pressure over a saturated solution of the compound. Above this relative humidity, the process that takes place is shown in Fig. 8.

If the vapor pressure in the atmosphere to which the solid is exposed is higher than the saturation pressure, moisture will condense onto the solid (a), which will dissolve in the condensed water (b). The condensation will continue (c) until a solution is formed that has the same vapor pressure as the atmosphere (d). In this case, hence, the end result is a liquid, and this is referred to as *deliquescence*.

The more soluble a substance, the lower the relative humidity over a saturated solution, so that the more deliquescent it is. The other component of hygroscopicity is the *rate with which the moisture adsorbs*. Most substances have solubilities such that the deliquescence RH is above 60%. It is a good idea to assess how soluble a substance would have to be to have a deliquescence point of 60%. Say the molecular weight is 150, and suppose the solubility is 300 mg/ml (i.e. the molefraction is $2/(55.5+2) = 0.036$ mole fraction). In that case, the relative humidity over a saturated solution would be 96.4 %RH (i.e., even with rather soluble substance it is unlikely that the deliquescence point is reached). The calculation assumes ideality, and often that is not the case, so that actual deliquescence values *will* be lower. At elevated temperatures, solubilities, in general, increase, and if one asked at what solubility would there be deliquescence at 40°C and 75 RH, the so-called Joel Davis test (12), the answer would be as shown below:

If the solubility is denoted X_s molefraction, then $(1-X_s) = 0.75$:

$$X_s = 0.25 = x/(x + 55.5), \tag{12}$$

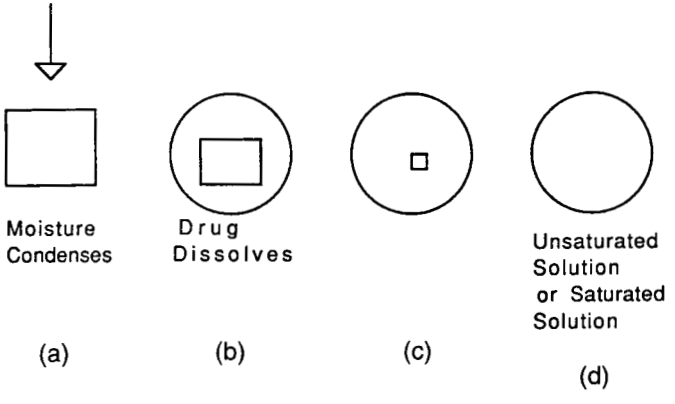

FIG. 8. Schematic of vapor adsorption onto a solid.

where x is moles of drug substance per 1000 g of water. Hence:

$$0.75 \times = 55.5 \times 0.25 \text{ or } \times = 18.5 \text{ moles/liter} \quad (13)$$

Again, this assumes ideality, and actual solubilities required are probably less. Similar considerations hold for hydrates.

B. Hygroscopicity in General

Below the deliquescence relative humidity, the amount of moisture sorbed is a function of a conventional isotherm, usually a BET isotherm. If a solid dosage form is dried to a certain "moisture content" (average, expressed in g of water per g of solid), then there will be, on subsequent storage, an exchange of moisture between solid components of the dosage form. Fig. 9 shows the isotherms for a two component system (which could also be a drug *product* and a desiccant bag). If a product containing only A and B were made and dried to 5% moisture (y = 0.05), then A would require a relative humidity corresponding to the point C and B corresponding to a point D. Because it is not possible to have two different relative humidities in a confined (e.g., pore) space, B will give up moisture (to point F), and A will pick up moisture (to point E), so that their moisture contents will change to yield a common relative humidity. In Fig. 9, this occurs at a = 0.28 or at 28% relative humidity.

VII. DIFFUSION THROUGH POLYMERS

One of the most important factors in stability is moisture. From a pharmaceutical point of view, the bottling of pharmaceuticals is of great importance. Until

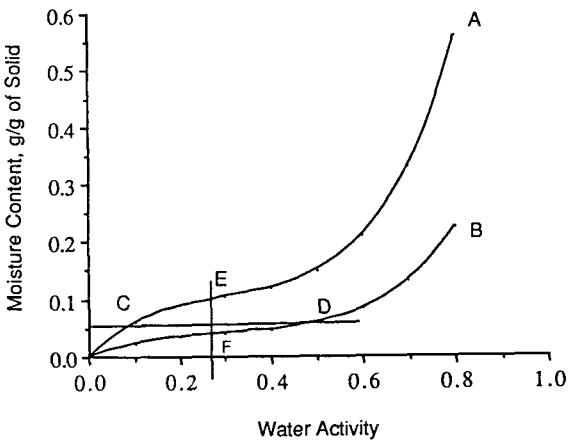

FIG. 9. Isotherms for a two-component system.

the late 1960s, drug products were stored and sold in glass containers, but with the advent of sufficiently impermeable plastic bottles, these offered sufficient advantages (cost, brittleness, freight cost) and gained popularity. The problem of stability now became twofold: (a) how stable the product is in the presence of moisture and (b) how long the bottle can keep the moisture sufficiently low without exceeding the critical moisture content.

A. Measurement of Diffusion Coefficients

Diffusion coefficients for gases through plastics can be determined by so-called Dow cells (Fig. 10). Stopcock A is first opened allowing evacuation of the system, and this gives rise to a barometric leg in the manometer. As soon as A is closed, gas will diffuse through the membrane (without now being sucked out by the vacuum), and the mercury (or other liquid) level will decrease. The level can be monitored as a function of time, converted to volume (or mass, by the gas law) and treated as follows.

The rate of penetration is given by:

$$dM/dt = AD(C_{s1} - C_{s2})/h \tag{14}$$

where M is the amount of gas diffusing through, t is time, A is the surface area of the film, h is the film thickness, and D is the diffusion coefficient (6,13). The terms C_{s1} and C_{s2} are the concentrations of gas in the film at the stream side and at the manometer side, respectively. The film, in this view, is considered a liquid phase, so that by Henry's law:

$$C = K_h P \tag{15}$$

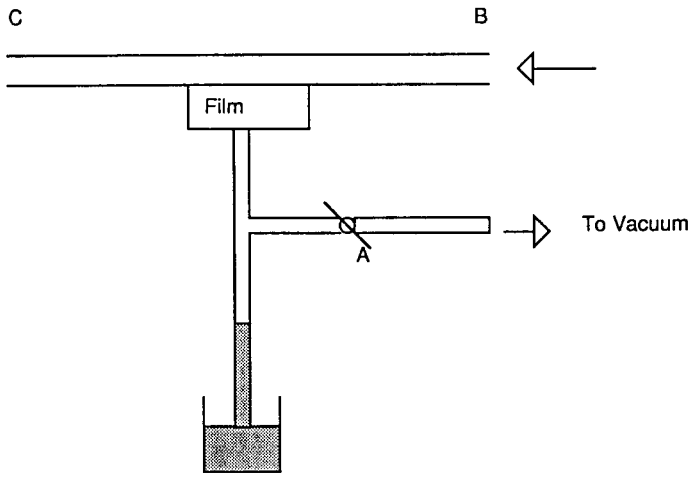

FIG. 10. Principle of a Dow cell.

where K_h is Henry's law constant and P is vapor pressure, so that:

$$dM/dt = ADK(P_1 - P_2)/h \quad (16)$$

The constant DK is often denoted Π and is called the permeability:

$$\Pi = KD \quad (17)$$

As mentioned, the height of the mercury level in the manometer is monitored. Knowing the diameter of the manometer tube allows easy calculation of V, which is then converted to M by the gas law, allowing plotting according to Eq. 16.

B. Diffusion into an Empty Bottle

If an empty, plastic bottle containing no moisture at all were placed in an area where the moisture vapor pressure were P_1, then moisture would start moving into the bottle in accordance with the previous equations.

At a given time, t, the vapor pressure on the inside of the bottle will be P_2. This is given by (noting that the number of grams of water is $n \times 18$, where n is the number of moles):

$$P_2 = (M/18)RT/V \quad (18)$$

where V is the volume of the bottle. Hence:

$$dM/dt = \{(18V)/RT\}\, dP_2/dt \quad (19)$$

Using Eq. 16 now gives:

$$\{(18V)/RT\}\, dP_2/dt = ADK(P_1 - P_2)/h \quad (20)$$

or

$$-d(P_1 - P_2)/(P_1 - P_2) = \{ADKRT/(18Vh)]\, dt \quad (21)$$

which integrates to:

$$\ln(P_1 - P_2) = -Ft + \ln(P_1) \quad (22)$$

where

$$F = \{ADKRT/(18Vh)] \quad (23)$$

Eq. 22 may be written:

$$P_2 = P_1[1 - e^{-Ft}] \quad (24)$$

which has the shape shown in Fig. 11.

If plotted according to Eq. 22, the data will take the form shown in Fig. 12.

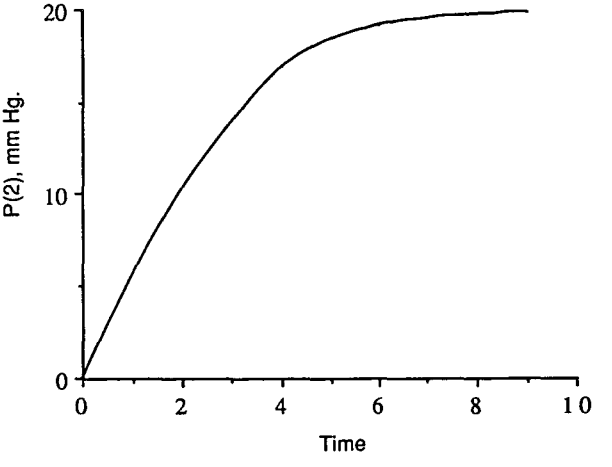

FIG. 11. Interior vapor pressure as a function of time of a bottle placed at 25°C and 80% RH (P_{H20} = 20 mm Hg).

C. Diffusion into Filled Bottles

The diffusion of gas (moisture) into an empty bottle allows calculation of the diffusion coefficient, D (or the permeation coefficient, KS), and as such allows comparison of the relative moisture barrier properties of various plastics and bottle configurations. However, from a point of view of what actually happens to a dosage form in a bottle, the considerations are slightly different.

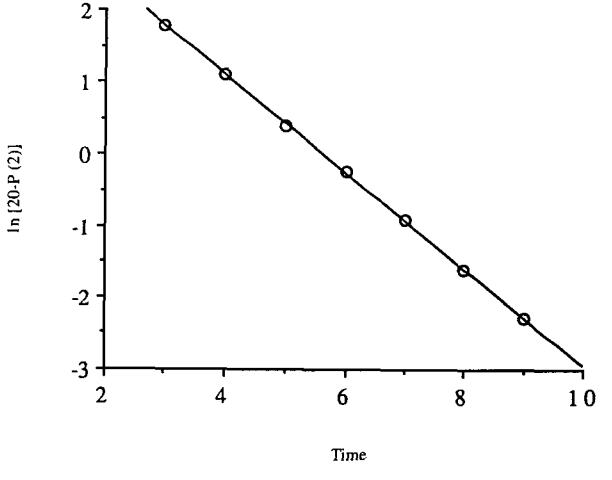

FIG. 12. Data from Fig. 11 treated according to Eq. 22.

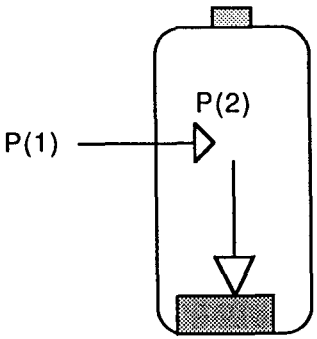

FIG. 13. Schematic of moisture permeation into a bottle containing drug product or drug substance.

The situation of moisture transfer from a vapor pressure of P_1 on the outside of the bottle to the inside, where the pressure is denoted P_2 is depicted in Fig. 13. The situation refers to a blister as well, except here the closure would be the seal.

Diffusion of a gas (e.g., water vapor) through a film of thickness, h, and diffusion coefficient, D, is given by Eq. 13 and equating this with Eq. 18:

$$\{(18V)/RT\}\ dP_2/dt = ADK(P_1 - P_2)/h \tag{25}$$

The solid possesses a specific moisture isotherm, and in the simplest of the Peppas models (14), it is assumed that this is simply a linear function (Fig. 14).

$$P_2 = Qx \tag{27}$$

where Q is a constant and x is g of moisture per g of solid. Hence:

$$dP_2/dt = Qdx/dt = \{ADKRT/(18h\ V)\}(P_1 - P_2) \tag{28}$$

Peppas used more realistic isotherms in computer simulation of moisture intrusion data in packages, but the simple model can be solved in closed form. Combining Eqs. 8.27 and 8.28 now gives:

$$dx/dt = \{ADKRT/(18hQV)\}(P_1 - Qx) = F(\beta - x) \tag{29}$$

where

$$F = \{ADKRT/(18hV)\} \tag{30}$$

and

$$\beta = P_1/Q \tag{31}$$

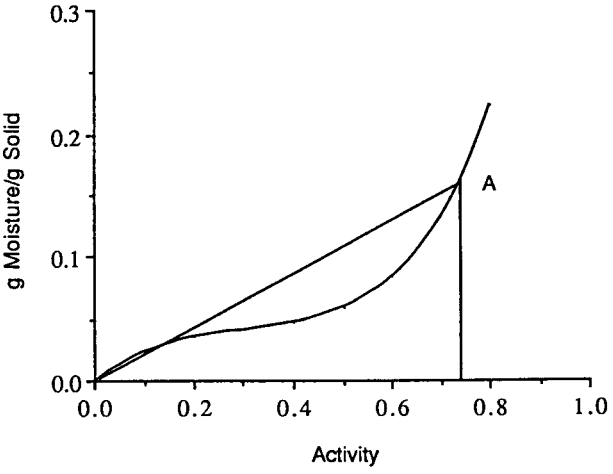

FIG. 14. Approximation made in the first Peppas model.

Eq. 30 rearranges to:

$$dx/(\beta - x) = Fdt \tag{32}$$

or

$$\ln(\beta - x) = -Ft + \ln(\beta) \tag{33}$$

or

$$x = (\beta)[1 - e^{-Ft}] \tag{34}$$

From the definition of F it is obvious that the rate of uptake is larger (a) the larger D is, (b) the smaller V is, (c) the larger A is, and (d) the smaller h is. V is here the void space in the bottle (i.e. the volume of the empty bottle minus the volume of the tables or capsules in it). It is also noted that at infinite time:

$$x_\infty = \beta = P_1/Q \tag{35}$$

i.e. via Eq. 8.19 the consequence is that $P_1 = P_2$, as indeed should be the case. The trace of x versus t is of the same nature as those shown in Figs. 8.5 and 8.6.

It can be shown, that with a better approximation of the BET-isotherm the equation becomes:

$$x = (\beta)[1 - e^{-Ft}]^{1/2} \tag{36}$$

and Peppas (14) with computer simulation, has shown even better fits to actual moisture isotherms. Curves of this nature will have profiles of the type shown in Fig. 11.

VIII. MOISTURE UPTAKE RATE CONTROLLED STABILITY

In cases of substances that do not adsorb moisture very rapidly, the limiting situation is one in which the vapor pressure in the bottle will not be governed by the moisture content in the tablet or capsule, but rather the pressure, P_2, will build up until it reaches its equilibrium value, P_1 (the outside vapor pressure), before the dosage form has adsorbed sizable amounts of water. In such a case, the moisture content, x (fraction), of the dosage form will increase, approximately, by the relation:

$$dx/dt = kA(P_1 - Qx) \tag{37}$$

where Eq. 27 has been invoked in the last step.

This may be rewritten:

$$dx/(\alpha - x) = kAQdt \tag{38}$$

where

$$\alpha = P_1/Q \tag{39}$$

Eq. 38 integrates to:

$$\ln(\alpha - x) = -kAQt + \ln(\alpha - x_o) \tag{40}$$

where x_o is the moisture content of the dosage form at the time it is introduced. Eq. 40 can be written:

$$x = \alpha + (\alpha - x_o)e^{-kAQt} \tag{41}$$

or if the material is completely dry at the onset:

$$x = (P_1/Q)(1 - e^{-kAQt}) \tag{42}$$

which gives a curve similar to the one shown in Fig. 11. It shows that moisture adsorption rate (i.e., loss of stability or suitability) increases (a) the higher the outside relative humidity, (b), the smaller the absorption isotherm constant (Q), (c) the larger the specific surface area of the drug (the finer it is), and (d) the larger the adsorption rate constant, k, is. For this reason, many investigators also check the behavior in open Petri dishes of the dosage form and the drug substance under the same accelerated conditions as they test the drug product in the bottle. The situation, just described, essentially states that the bottle as a barrier does not count, and for certain, nonhygroscopic materials (or materials with a low adsorption rate constant), this can be correct.

IX. EFFECT OF BOTTLE CONFIGURATION

It should be noted that if a bottle is considered to be isometric, then the area is given by a shape factor, Γ, times the 2/3-power of the volume, and in this case the equation for F may be written:

$$F = \{DKRT\Gamma/(18hV^{1/3})\} \quad (30)$$

In other words, the larger the bottle, the smaller F is (i.e., the more stable the product will be). This is in line with the general finding that blisters, as far as moisture permeation is concerned, is the most susceptible package.

Another consequence is that if a certain number of tablets is in a bottle and the bottle size is increased (more head space), then the rate with which the dosage form takes up moisture is smaller.

Again, V is the free volume in the package, so that a "tightly" packaged solid dosage form will allow for more rapid moisture pick-up than a loosely packed dosage form.

X. EFFECT OF DESICCANT

The shelf life of a moisture-sensitive product can be prolonged by means of desiccants. If, as shown in Fig. 15, the drug product has a critical moisture content of A%, and a certain amount, M, of desiccant is added, then as moisture penetrates the bottle, both desiccant and dosage form will adsorb moisture. At any given time, the relative humidity is given, so that the moisture content can be deduced from the relative humidity in the bottle.

When the relative humidity is 20%, the critical moisture is reached. At this point, the moisture in the desiccant has risen from zero to 15% per weight (point C). If Q gram of dry desiccant is used to start with, then (0.15 × Q) grams of water are allowed to penetrate the bottle without the dosage form going beyond its critical moisture content.

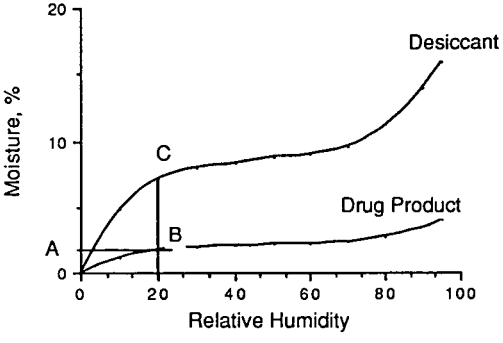

FIG. 15. Isotherms of drug and desiccant in a bottle.

If the moisture penetration rate is m grams per day, then the prolongation of shelf life would be 0.15 Q/m days. It is noted that this prolongation is a function of the desiccant used (the isotherm) and of the amount of desiccant used. If the critical moisture content and permeation of the container are known, the necessary amount of desiccant can be calculated by this procedure.

Desiccants at times, in the early storage in a humid atmosphere, will dry out the product faster than the moisture penetrates, and this can be detrimental to the stability (e.g., could dehydrate a hydrate). This factor should always be considered in the choice of desiccant.

XI. TESTING CONDITIONS

The ICH-guidelines require the following:

Tier 1. Samples will be placed at "room temperature", which now will be defined as 25°C ± 2°C and 40-60 % RH. Testing periods will be 3, 6, 9, 12, 18, 24, 36 (48) months.

Tier 2. Samples will be placed for 3 and 6 months at 40°C, 75% RH. (Davis, 1982)

Tier 3. Samples will be placed for 3 and 6 months at 30°C, 60% RH.

In principle, only the first two tiers are necessary, **but**, the requirement is that if tier 2 shows "any significant change", then tier 3 must be effected. Since storage at 40°C, 75%RH will **always** cause some significant change (disintegration, dissolution, potency), then, if tier 3 were not started at the onset, there would be no way of putting it into effect. "Any significant change" refers to falling outside specifications.

A. Summary

1. For liquids this is primarily moisture loss through the container, leaching and drug loss by mass transfer, considering the package an individual phase and applying the partition law.
2. For interaction of liquid products with metal containers, moisture is of great importance.
3. For moisture induced stability problems for solid dosage forms in plastic containers, the principles of moisture penetration have been outlined, and the effect of the bottle geometry and the properties of the plastic have been touched on.
4. Leaching in the case of bulk stored tablets or capsules has been discussed.

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Containment Facilities for Production of Clinical Supplies

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I. INTRODUCTION

Processing of clinical supplies for most therapeutic categories requires facilities designed and engineered to prevent product cross-contamination in a controlled environment. Although some activities may require specialized masks or breathing apparatus, the majority of products can be safely manufactured while wearing reusable uniforms, safety glasses, gloves, and standard dust masks. Cleaning of equipment and processing rooms is accomplished by use of aqueous detergents followed by final rinse with deionized water.

Safe production and handling of antineoplastic (cytotoxic) drugs, however, require that work be done in special facilities whose main engineering features are based on considerations for workers' health and welfare and complete environmental protection. With these goals in mind, the best approach when planning construction is to design facilities that control the level and containment of airborne contaminants as they are generated, and have the capability of holding aqueous effluent from containment drains until its deactivation/degradation is assured. Protection provided by special clothing and breathing apparatus, although important, should be secondary to that of facility design.

This chapter presents practical information for those who are already involved with production or handling of antineoplastic clinical supplies, as well as those who may be considering construction of a suitable facility in the future.

II. ENVIRONMENTAL PROTECTION

A. Containment and Neutralization (Deactivation) of Aqueous Waste

When dealing with potentially carcinogenic compounds, facility design becomes a bit more complicated because of environmental concerns. Although government regulations for waste water do not list specific compounds, regulations specify that waste water should be free of any mutagenic/carcinogenic activity.

In plants in which antineoplastic or other classes of compound present a threat to the environment, it is imperative that waste water be collected in a

reservoir for further processing before sewering. This is especially true for a clinical manufacturing facility where several compounds or formulations may be prepared simultaneously in separate areas, thereby producing aqueous effluent whose final composition and activity are unknown.

Floor and sink drains from containment areas have to be connected to a main reservoir that is surrounded by a trap. The reservoir (double shell design, resistant to high or low pH) should be situated above ground or in an accessible underground room where it can be routinely inspected for leaks or cracks. The surrounding trap, made of impermeable cement, should be designed to hold sufficient volume to contain any accidental spills or leakage. In facilities in which production of different antineoplastic agents changes frequently, it is preferable to subdivide the main reservoir into several compartments. This permits pumping a known volume whose contents can be better identified, thereby adding more certainty to the appropriate method of decontamination. Continuous monitoring of reservoir levels can be provided by level sensors whose set points, if exceeded, activate audible alarms and printouts in the maintenance area, as well as the site's off-hour monitoring station.

When designing the plumbing, it is important to carefully separate sanitary/restroom drain pipes from those going to the containment reservoir. If this is not done, the reservoir will be contaminated by bacterial waste, or the sanitary drain may contain untreated, potentially toxic compounds.

Some equipment (e.g., autoclaves, stopper washers) use large volumes of water during normal operation. Wherever possible and with consideration for environmental impact, their piping should go directly to the sanitary drain. Otherwise, the containment reservoir will be subject to frequent, unnecessary overload.

When the containment reservoir (or one of its compartments) is full, its contents can be transferred to the treatment tank. Preliminary samples (pretreatment) can then be tested for pH conductivity, turbidity, etc. An estimate of potential contamination load can be made by maintaining a logbook of production activities to note the time, since the previous treatment or tank flushing was performed. Unaccountable production losses for each batch, when added together, should provide a good indication of how much drug substance is present for decontamination/deactivation. Depending on the amount of active material present and its chemical composition, a validated decontamination method will be performed. Chemical parameters will again be taken to verify that the waste water is within acceptable limits. Required tests include chemical oxygen demand (COD) and biological oxygen demand (BOD). Upon receipt of test results, if within limits, the waste water can be sewered. If analytical methods have been developed, the possibility exists for measurement of any residual drug active still present. Further action can then be taken, as needed, before sewering.

Information gathered during deactivation and testing of the facility's aqueous effluent may be subject to governmental or corporate audit for compliance with environmental protection regulations. Therefore, it is important to keep an accurate and complete logbook of all critical data.

Methods for decontamination of antineoplastic agents have been published (1). Fortunately, general methods were developed for both antibiotic and metal complex type drugs, the two most common classes of product.

B. Safe Disposal of Organic or Solid Waste

Because antineoplastic agents are, themselves, potential carcinogens, (1–5), the use of disposable gowns (hoods, coveralls, boot covers, masks, and gloves) is recommended. In some cases, it may be possible to decontaminate reusable garments by validated methods. However, management must be aware of the increased risk this poses to workers' health and welfare.

Disposal of used gowns and solid materials is tedious and highly regulated. Special containers, provided by government-approved disposal companies, must be packed according to rigid standards. If these containers are stored on the premises until there is sufficient quantity to warrant pick-up, the storage area must meet all applicable standards for environmental safety.

Incineration is the method of choice for destruction of antineoplastic contaminated waste products, and this should be made clear to the disposal company. In fact, the responsibility for proper destruction of waste materials rests with the company that produces the waste, not the disposal company.

C. High Efficiency Particulate Air (HEPA) Filtration of Exhaust (Return) Air

Another way that the environment could be adversely affected is by air coming unfiltered from a contaminated area. To prevent this, the facility design should focus not only on the incoming air, but also on air returned to the environment. Critical areas where "active" powders are produced or handled should have HEPA-filtered low return air ducts. If processing tends to generate dust, a prefilter can be installed upstream to prevent premature blocking of the HEPA filter.

Rooms situated near areas where dust is generated may have lower air pressures than those where the dusty operation is being performed. If so, these rooms should also be equipped with HEPA filters on the air exhaust plenum. Design features should include ease of testing and replacing of filters, as needed. Cold dioctylphthlate (DOP) and air velocity tests should be performed at least annually to confirm absence of filter leaks or changes in volume of air supply.

As an added safety feature, one should consider installing a second HEPA filter on the facility's main exhaust. This filter will probably be located in a

noncontaminated zone and, therefore, to maximize worker safety, should feature bag-in bag-out filter change. Although the facility may have dual HEPA filtration, recirculation of exhaust air from containment zones is questionable practice and one-pass air systems are recommended. One area in which an exception might be considered, however, is the sterile room. If the product is a liquid fill, generation of airborne product particulates should be low, thus making recirculation of air through HEPA filters feasible and cost efficient.

Some equipment, such as lyophilizer vacuum pumps, vents on the main waste water reservoir or treatment tank, and others may require connections to the HEPA filtered exhaust. These additions put considerable strain on exhaust fans and must be accounted for during facility design.

III. WORKER PROTECTION AND TRAINING

A. Training of Facility Staff, Including Maintenance, Quality Control and Contract Equipment Repair or Calibration Technicians

All personnel whose activities are performed in areas of potential exposure to toxic substances must be trained in safe handling techniques and should receive appropriate information such as that provided in MSDS (Material Safety Data Sheet) documents before starting their work. Training must include proper course of action to take if accidental exposure occurs.

Facility staff should hold periodic safety meetings to review existing procedures and identify any areas of deficiency or need for update resulting from change of process or procedure. These meetings should be attended by Maintenance, Quality Control, or other personnel who may occasionally be called on to work within containment areas.

Contract equipment repair or calibration/validation technicians may be reluctant to perform essential tasks when told that they must follow gowning procedures and shower at the conclusion of each work shift. Accordingly, they should be advised of special working conditions, offered adequate training, and be told that compliance with facility standards of safety are mandatory before they can receive a purchase order for their services.

B. Special Gowning and Safety Apparel

Work in containment facilities requires that protective clothing be worn at all times. Degree of protection afforded by various types of gloves and disposable clothing fabric has been the subject of several published reports (4,6). Unfortunately, fabrics that provide the most protection are usually the least comfortable, and, therefore, choice of garment may be a balance between worker acceptance and the necessary level of protection. In practice, workers remove street clothes, including shoes, and leave them in lockers outside containment

zones. They then don protective clothing and equipment over their undergarments. Rings, watches, jewelry, and cosmetic make-up should be removed before entering areas where toxic materials may be present. Each worker should be provided with a pair of facility-dedicated shoes.

Protective clothing suitable for *nonsterile* production/batching or laboratory activities may include:

1. Disposable Tyvek-brand or other dust-impermeable coverall suit, including attached hood or separate protective headpiece.
2. Disposable protective shoe covers/boots
3. Disposable latex or nitrile gloves
4. Dust mask or other appropriate respiratory protection, as needed
5. Chemical safety goggles or face shield, as needed

When working with solvents, special consideration should be given to the use of respirators designed to protect from vapors, and also, butyl rubber sleeves to protect from splashing or liquid spills.

Sterile area work necessitates the donning of a sterile gown (including shoe covers, hood, and surgical mask) over the clothing listed above for nonsterile activities. As this adds to the discomfort of sterile area workers, the temperature, at least in the sterile filling room, should be approximately 5°C lower than in nonsterile areas.

C. Medical Surveillance

Employees who are potentially exposed to anticancer materials should participate in an appropriate medical surveillance program.

Case reports (2) of adverse reactions to limited occupational exposure to antineoplastic agents in a hospital setting give ample warning of the toxicity of these compounds. Although the protective measures provided to pharmaceutical workers through total gowning, plus sophisticated engineering features of the facility itself, unquestionably give better protection than would be found in most hospitals, the hospital worker is handling commercial products whose potency may be a fraction of that handled by those who work with the undiluted active drug substance. Also, the hospital worker may be exposed periodically during the course of duties, whereas the employee assigned to work in a containment facility is potentially exposed during each work shift.

To be meaningful, a medical surveillance program should include a preplacement examination, periodic monitoring for changes in original, baseline examination data, tracking of employee illness patterns, and an exit examination when the employee no longer works in the facility (7). In addition to complete annual physicals, each employee should receive 6-month monitoring that includes complete blood count plus differential. Other procedures and tests should be conducted on an individual basis and at the discretion of the exam-

ining physician. Any employee who suspects that an adverse health condition was caused by contact or exposure to an anticancer agent must notify his/her supervisor and appropriate medical authorities.

D. Decontamination of Rooms/Equipment Before Shut-Down for Major Maintenance or Renovation/Expansion

When major maintenance or renovation/expansion of a containment facility is being considered, careful thought must be given to the potential danger this poses for those involved with the work. In most cases, it would be very impractical to expect maintenance or construction workers to carry out their tasks in full gowning, with gloves and masks or respirators. A better alternative, and one which is usually taken, is to deactivate/decontaminate all equipment, areas and, if possible, heating, ventilation, and air conditioning (HVAC) ductwork that affects the zone where work is to be done. Extent of the work will help determine whether HVAC ductwork should be temporarily blocked or completely removed and replaced.

Utilization/Activity logbooks, which give a chronological record of clinical production activities for rooms and equipment, provide guidance about what substances may be present in trace quantities. Once this is known, protocols can be written, approved, and enacted to ascertain that it is safe for maintenance or renovation/expansion work to begin.

E. Emergency Spill Response

Accidental spillage of antineoplastic drug outside a Biological Safety Cabinet must be regarded as an emergency situation. When an accident happens, the following steps (as appropriate to the scope of the spillage) should occur:

1. Immediate evacuation of employees working in the vicinity of the spill and appropriate first aid, if called for. Follow-up medical attention as necessary or recommended in the Material Safety Data Sheet for the substance spilled
2. Immediate notification of area supervisor and Environmental, Health and Safety personnel
3. Immediate notification of facility or departmental spill response team who will:
   a. Don appropriate personal protective equipment
   b. Retrieve a Spill Clean-up Kit (contents listed below)
   c. Clean up the spill, deactivating and removing residue
   d. Prepare the spilled material for safe disposal
   e. Swab test the cleaned area for presence of residue (if validated cleaning procedure is available)
   f. Decontaminate and/or dispose of personal protective equipment
   g. Complete the Spill Clean-up Kit checklist and report the spill event

Spill Clean-up Kit

Items recommended as essential components of a Spill Clean-up Kit include the following:

1. Complete set of disposable clothing for overgowning
2. Respirator with chemical cartridges appropriate for solvents used
3. Goggles/safety glasses and gloves
4. Sponges and absorbent towels
5. Plastic bags and wire tie wraps
6. Wet/dry vacuum cleaner equipped with a HEPA filter
7. Disposable scoops or similar devices to collect spilled solids
8. A biohazard disposal pouch or other rigid container for sharp objects such as broken glass, needles, etc.
9. Container with deactivation/decontamination solution (this should be present during handling of anticancer substances so that it's already available, if needed)
10. A rigid container for use as final disposal container for contaminated waste
11. Pen and Spill Event checklist to record steps performed and signatures of those who performed them

F. Emergency Contingency Planning

All facilities where drug products are produced should have specific plans for proper response to emergency situations. In the case of containment facilities, however, uncontrolled release of substances could be life-threatening or have significant impact on the environment.

Therefore, it is important to have contingency plans ready in case disasters occur. Because firemen are often called on to handle these situations, they should be told where active materials are stored and which rooms or zones are potentially contaminated. Also, there is a need to assign someone on site as the person responsible for coordinating responses to emergencies. A 24-hour emergency phone number should be displayed prominently near facility telephones.

IV. LAYOUT OR FLOOR PLANS

A. Oral Product Operations

Physical layout and engineering features of work zones where oral dosage forms of antineoplastic products are manufactured require special considerations. Processing steps, such as weighing, blending, screening, tabletting, and encapsulating, are all potential dust generators. If not properly controlled, the dust could reach other areas of the containment facility, increasing risk of product cross-contamination.

There are three primary ways to control or contain airborne contamination during dusty operations:

1. Low return room air, HEPA filtered
2. Room and corridor air pressure differentials
3. Airlocks between zones

The installation of low return, wall-mounted, HEPA-filtered air ducts, where supply air enters the solids cubicle (Fig. 1) from a corner ceiling plenum, provides an air-sweep effect, removing dust as it is generated. By maintaining a corridor air pressure that is higher than that of the solids cubicles, dust is less likely to escape. As added protection, a series of airlocks can be installed to separate oral product production, centralized laboratory, and sterile operations zones, each of which has its own unique containment requirements. Air pressure balance in each room, airlock and corridor can be maintained by computer controlled sensors that regulate opening and closing of dampers in the supply ductwork. Doors inadvertently left open would cause an imbalance that the computer would be unable to correct. Therefore, consideration should be given to installing an alarm system that provides a warning and identifies which door is open.

Other facility features depicted in Fig. 1 include:

1. *Pass-thru* between offices (noncontainment zone) and corridor in containment zone. This permits transfer of small items, properly enclosed/bagged, without workers having to gown or degown and shower.
2. *Unloading/loading dock with airlock.* By opening only one door at a time, the outside environment is protected from potentially contaminated air.
3. *Clean equipment storage.* Equipment that has been used in clinical production is cleaned in the Equipment Wash room. It is then dried and stored in an adjacent room without passing through the corridor.
4. *Offices outside containment area.* Offices, break rooms, and cafeteria are all situated outside containment zones. This eliminates the need to gown-up when entering these areas.

B. Parenteral Product Operations

1. Operational Flow

During the facility design phase, engineers and architects should work closely with the facility's eventual occupants to simulate the operational flow. Wherever possible, the goal should be to simplify and improve efficiency. It is especially important to differentiate between clean and contamination processes. For example, items must be clean and sterile when entering the sterile area. While there, they may come into contact with the product being processed. To be reused, they must undergo decontamination and cleaning before reentry into the "clean" glassware preparation area.

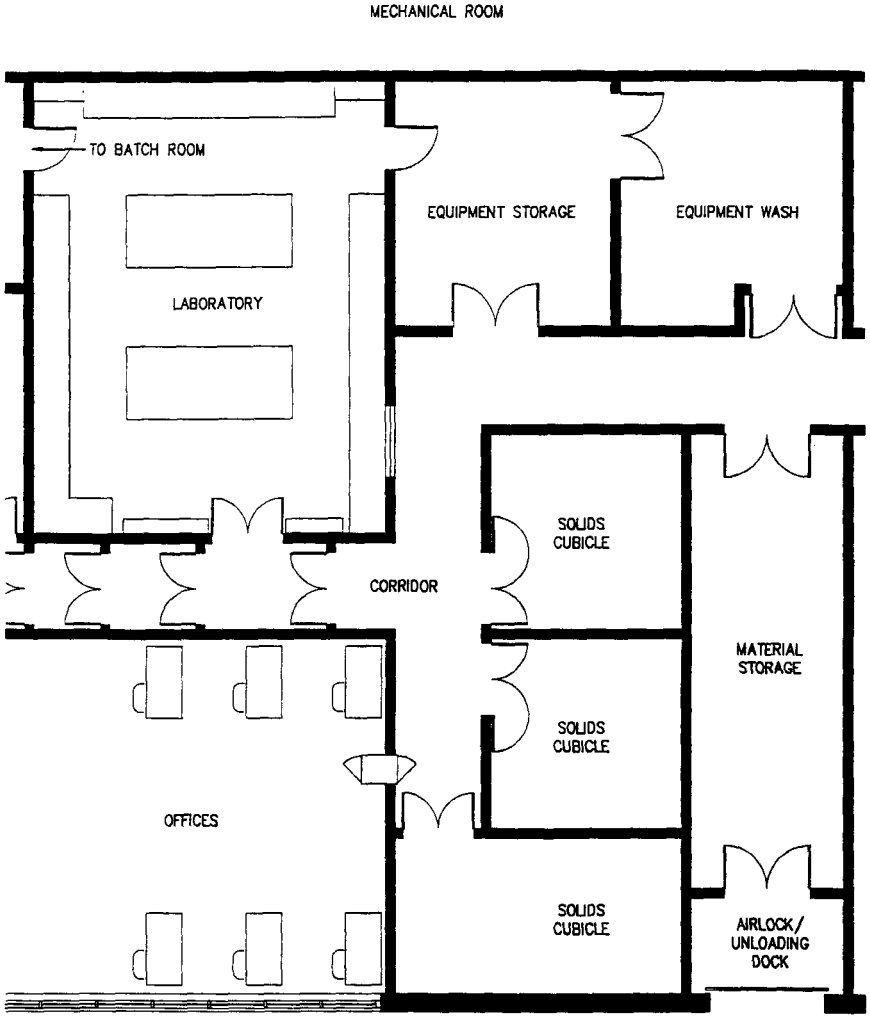

FIG. 1. A schematic floor plan of the oral product production cubicles, equipment wash and storage rooms, and laboratory within the containment facility. Airlocks at the unloading/receiving dock and within the containment corridor separate oral production, laboratory, and access to the sterile production zone.

Fig. 2 depicts the sequence of basic activities associated with preparation of a lyophilized product. Clean versus contaminated areas are clearly identified. Located between these areas is a double-door washer whose decontamination cycle pumps in the appropriate chemicals for deactivation of the anticancer

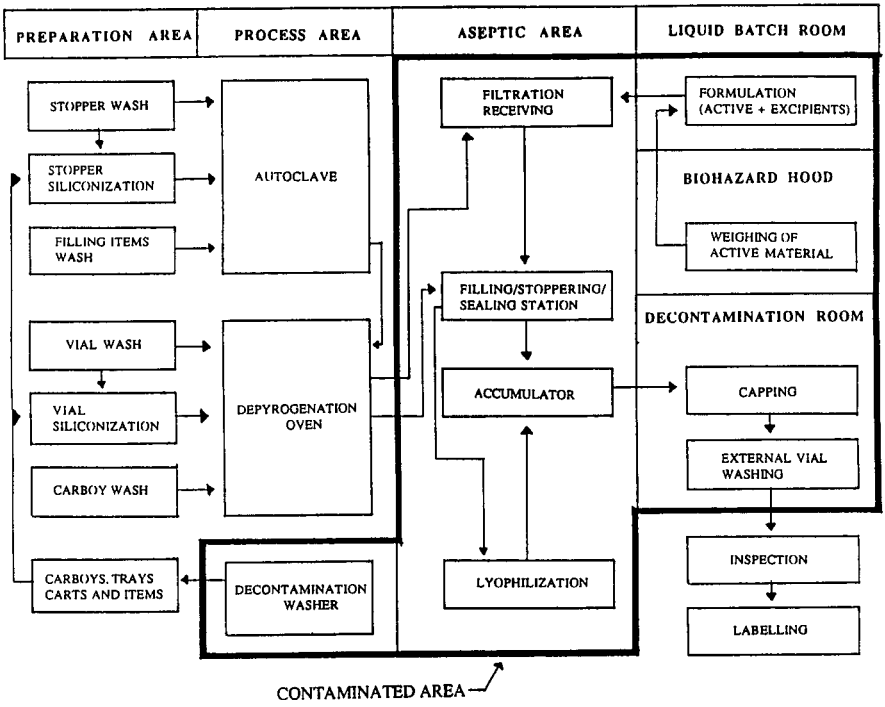

FIG. 2. The flow of activities performed during aseptic processing of a lyophilized product. Heavy dark boundary surrounds the activities performed within the containment zone.

compound present. Challenges using a variety of equipment loads and cycle parameters can be performed to validate the process for each class of anticancer product.

The lyophilizer itself presents concerns. Although some units are available with double doors, single door models would seem to offer the following advantages:

Elimination of another containment zone
Better containment if vial breakage or spillage occurs

At the conclusion of a lyophilization run, and before start of the next one, the interior chamber must be decontaminated and thoroughly cleaned. Because of the physical layout of a compact series of shelves, refrigerant lines and remote, hard to reach surfaces, clean-up can be tedious and potentially dangerous. For these reasons, units offering validatable CIP (Clean in Place) systems are highly recommended.

The third and last decontamination post within the parenteral operations area is located in the decontamination room. Finished product in stoppered vials enters the room via conveyor from the sterile filling room, and is then capped with aluminum seals. The capped vials then enter a washer/dryer where trace contaminants are deactivated and rinsed from exterior surfaces. Once dried, the vials are inspected and cartoned for storage pending complete analytical testing, labelling and release for clinical use.

2. *Sterile Suite Pressure Differentials*

Pressure differentials in conventional sterile suites are required by U.S. Federal Code 209B, which stipulates that pressure within the sterile filling room must be at least 0.05″ H_2O higher than adjacent rooms. This regulation is aimed at preventing viable particulates from nonsterile areas entering the sterile area. However, containment facilities must also address the problem of keeping toxic materials in the room where they are being processed, and this includes those in sterile areas.

Fig. 3 depicts one way this can be achieved. The pressurization system, controlled by a main computer, consists of pressure transducers that read each room's air pressure once per minute and give feedback signals to open or close return air dampers, as needed, to maintain proper balance. With this type of system, variance should not exceed 0.03″ H_2O from the set point.

By connecting a printer to the computer, room pressures can be recorded and printed for systems analysis or inclusion in clinical batch records. Also, an alarm (visual and/or audible) can be coupled with the pressurization system for monitoring sterile area differentials during sterile filling. This helps meet good manufacturing practice (GMP) requirements and, by monitoring the HVAC system, increases worker safety.

Other special design features include the following:

a. Separate Areas for Gowning and Degowning

Factors that make separation of areas for gowning and degowning advantageous are the following:

Gowning area is kept free of toxic contamination
Gowning and degowning processes require different levels of cleanliness
Two exits are provided for escape in case of emergency
One-way flow of workers to and from sterile room

One interesting aspect of the gowning area is that its air pressure is equal to that of the sterile filling room. In conventional gowning areas there would be a pressure drop. However, by adding an airlock between the gowning area and the sterile filling room, containment is achieved. This airlock is set at 0.03″ H_2O relative to the sterile room and, therefore, must meet Class 100 standards and

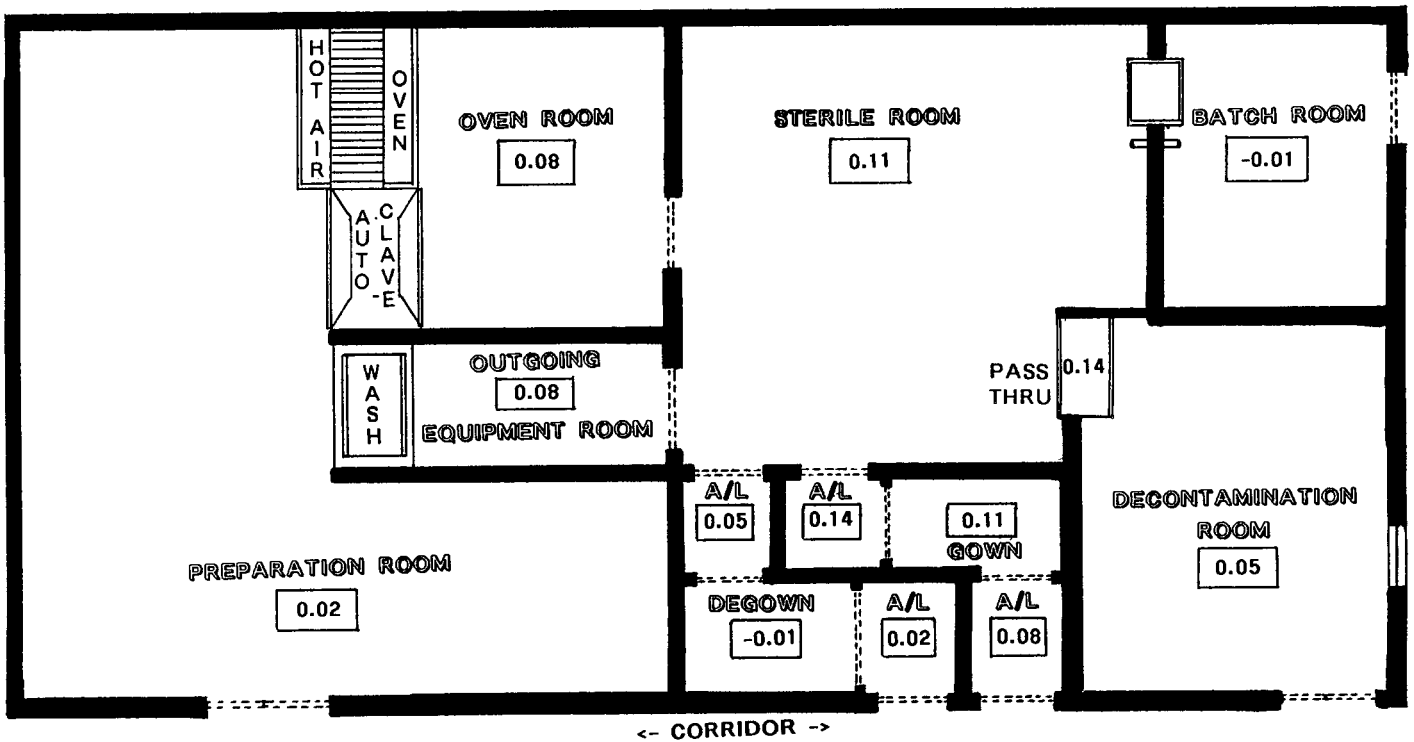

FIG. 3. Room pressure set-points within the sterile product work zone. Numbers within rectangular boxes represent inches of water and are identified as such within the text.

be closely monitored for bioburden. Another difference is the lack of a sink for hand washing. Because workers are already gloved, they use germicidal agents before donning sterile gloves.

The degowning area is designed to have the lowest pressure within the sterile suite so that any contamination resulting from collection of used gowns will be contained.

b. Oven Room for Unloading Autoclave and Dry-Heat Oven

Both the steam autoclave and the dry-heat depyrogenation oven are double-door pass-through units. They generate large amounts of heat, some of which transfers into the room when glassware and other materials are unloaded. Also, the unloading process increases particulates, especially if there is any glassware breakage. Therefore, by constructing a separate oven room adjacent to the sterile filling room, the filling room is more easily maintained at the proper temperature and particulate classification.

One drawback is the need to maintain the oven room at a slightly lower pressure (0.08″ H_2O) relative to that of the sterile filling room. This complicates matters from a containment standpoint and necessitates having a controllable pressurization system within the depyrogenation oven. Its setpoint is 0.15″ H_2O and, therefore, air from the oven room and preparation room is kept out at all times.

c. Pass-through for Transfer of Filled/Stoppered Vials for Capping

Transfer of the final product from the sterile filling room to the decontamination room is done by conveyor. A pass-through (airlock chamber, Fig. 4) is situated between the two rooms and, to prevent airborne contamination from entering the decontamination room, its air supply is HEPA filtered and controlled by a diffuser to maintain a pressure of 0.14″ H_2O.

V. SPECIAL CONSIDERATIONS

A. Hiring the Right People

Scientists, technicians, and support staff selected to work in containment facilities must be conscientious and careful when performing their duties. Employees who demonstrate a tendency to be accident-prone, who are under pronounced psychological stress, or who are frequently absent because of illness would be unsuitable for routine activities requiring great care and concentration. Their well-being and that of co-workers could be at risk.

Safety considerations often demand the wearing of face masks, respirators, or other special breathing apparatus when working with potentially toxic substances. Unfortunately, these protective devices are often uncomfortable or, in rare cases, impossible for some workers to wear. Therefore, it is important to

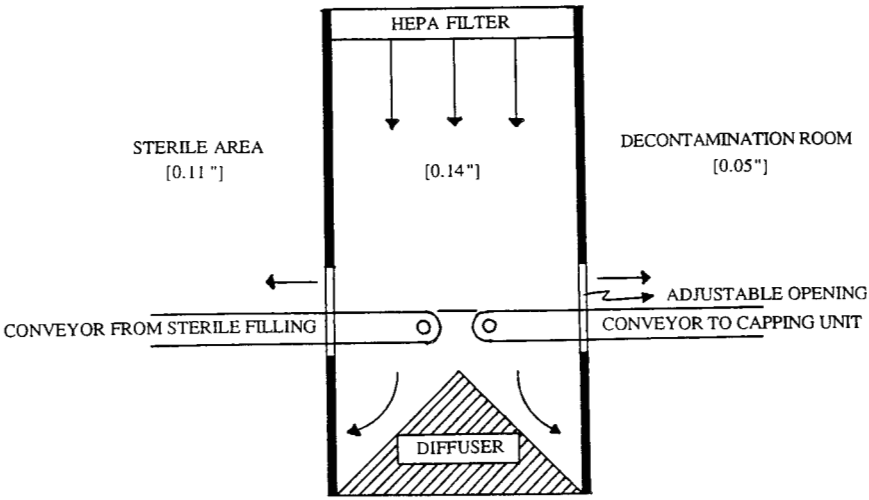

FIG. 4. Schematic drawing of the finished dosage pass-through between the sterile filling room and the decontamination room. Airflow is indicated by arrows to show that HEPA filtered supply air from the pass-through is diffused and sufficient in volume to block air from the sterile area entering the decontamination room and vice-versa.

conduct thorough evaluations of new staff members, eliminating, at the outset, those who cannot tolerate the wearing of these devices.

Because the majority of antineoplastic drugs manufactured for clinical use are sterile injectables in lyophilized or liquid form, clinical production staff must meet essential criteria for work in sterile areas. Those who have skin problems or other conditions or work habits that generate unusual levels of particulates would have to be reassigned. Also, because smoking is strictly prohibited in containment areas, those unable or unwilling to stop smoking might be disqualified from containment facility duties.

B. Data Transfer from Containment Areas

As much as possible, items that enter a designated contamination zone have to stay there unless there is a way to decontaminate them. In the case of batch or working documents that cannot be decontaminated, a suitable system has to be defined, implemented, and standardized. A major concern is the clinical batch record that contains essential manufacturing information. If documents must be brought into the containment zone, avoidance of contamination is virtually impossible, especially if the manufacturing process involves powders. If originals must remain inside, a means must be devised to transfer the information

to high quality copies whose content can be verified for completeness and accuracy. Ways to accomplish this, plus their pros and cons, are:

FAX: relatively easy, but there is a possibility of bad copies and missing information. Circular or strip chart data must first be photocopied before they can be transferred by fax.

COMPUTER ON A NETWORK EQUIPPED WITH A SCANNER: cumbersome and slow process, but usually good copy quality. This method requires validation of computer/software.

LAMINATION: seal the original document inside a hard plastic film. This is time-consuming and produces a thick file, but it does offer the original for review outside the containment zone.

PHOTOCOPYING: place each document in a clear plastic bag, then seal and decontaminate the bag's exterior. Photocopies can then be produced in clean zones. Alternatively, facility design permits installation of the photocopier so that copies made within the containment zone exit the photocopier into a clean zone.

An alternative to conventional paper systems is a paper-free system in which the manufacturing information, worksheets and other documents are available on software. The information can be sent electronically through a network to a terminal inside the containment area, where it is then processed and returned for upgrading or printing of hard copy. Some pharmaceutical companies have adopted and validated this type of system within regular production facilities. In theory, it would seem to be ideal for containment facilities as well. Whatever system is chosen, it is important that standard operating procedures (SOPs) be written and followed to prevent the accidental handling of contaminated documents by those who must review them for current good manufacturing practices (cGMP) compliance purposes.

C. Facility Lighting

Proper and adequate lighting are important aspects of containment facility design. Safety and security considerations for the nature of activities involved preclude the presence of exterior windows from containment zones. Therefore, all interior lighting must be artificial. Because many anticancer compounds are light-sensitive, the nature and intensity of light must be chosen on a room-by-room basis. Yellow light (fluorescent gold) with low level emittance of ultraviolet rays should be available in liquid batching, sampling, sterile filling, and finished dose packaging (exterior wash) areas. In addition, since yellow light provides a less desirable work environment, there should also be regular white fluorescent lights, with options of choosing either one or the other, or combinations of both, depending on the sensitivity of the compound/product present.

Lighting in areas where most of the ceiling surface is covered by HEPA filters must be provided by sources that do not disturb vertical laminar airflow. So-called "drop" lights, whose dimensions are less than 3 inches wide, 6 inches high, and up to 4 feet long are available for this purpose.

Because the fluorescent tubes will have to be changed periodically, access to them should be from noncontainment ceiling areas above the room illuminated. If access must be from the contaminated side, the tubes should be enclosed in a plastic sleeve so that accidental breakage would not release particles into a Class 100 room. Electrical switchboxes should be enclosed or sealed to avoid contamination and make cleaning easier.

D. Emergency Power Back-up

Loss of electrical power to a clinical supply containment facility poses two potential problems. First, lack of power results in shutdown of ventilation, disrupting room pressure differentials and, thereby, creating an environment where any airborne contaminants are no longer removed by HEPA filtration. If this occurs during the workday, operations must cease and personnel in containment areas must evacuate the facility until power is restored and room pressure differentials are within safe limits.

Depending on length of power interruption (and work in progress), sterile rooms might require re-fogging before resumption of activities. SOPs should be written to give guidance and proper course of action to cover this, as well as other emergency situations.

The second problem concerns the high expense usually associated with loss of antineoplastic compounds in general and in-process clinical supply batches in particular. Although initially expensive, a diesel-powered emergency generator will probably justify its cost the first time a power failure occurs when a clinical batch is in the lyophilizer.

E. Biological Safety Cabinets

During the course of clinical supply production, there are some activities that require the use of biohazard hoods. These activities include:

Sampling bulk drug substance
Weighing bulk drug substance
Testing of product containers
Removal of closure(s) from container(s)
Filter integrity bubble point tests

One type of approved unit is the Class II, Type B Biological Safety Cabinet with bag-in bag-out HEPA filter change capability. Cabinets with this classification are designed to protect worker, product, and environment (7). They

feature an open front with inward air flow at working surface level to protect the worker, HEPA filtered vertical laminar flow to prevent product contamination, and HEPA filtered exhaust air for protection of the environment.

Because air flow may not be uniform throughout the cabinet (especially if containers or equipment are present), tests should be conducted to establish proper placement of balances to guarantee accuracy when weighing bulk drug substance.

F. Transfer of Product Solutions

Production of sterile products usually involves several steps in which solutions containing drug substance must be transferred from one container to another. If the transfer involves pressurization, there is serious concern for partial aerosolization or misting. Therefore, filters should be installed at pressure relief points and/or the venting should be connected to an exhaust duct.

Passage of solution through sterilization filters in the sterile area (see Fig. 5) can be accomplished by peristaltic pump or pressurizing the transfer tank with an inert gas such as nitrogen. If a peristaltic pump is chosen, transfer tubing must be flexible. Unfortunately, flexible tubing is more prone to rupture, especially if filter blockage causes back-pressure.

The use of pressure displacement requires sanitary (or equivalent) connections that are leak free and transfer tubing that is either braided or double-shielded with stainless steel. Alternatives such as rigid Teflon or stainless steel tubing may be considered. In any case, compatibility of product with transfer tubing must be proven to meet GMP requirements.

Other considerations involving liquid transfer are the following:

Enclosure of capsule filters in stainless steel housing to contain leaks
Bubble point testing within vertical-flow biohazard hoods to protect workers from aerosol exposure

VI. BARRIER (ISOLATION) TECHNOLOGY

An alternative to conventional clean-room processing utilizes barrier technology. Already popular in Europe, this technology involves construction of airtight flexible "tents" or rigid boxes in which sterile operations can be accomplished by workers who remain outside the sterile environment.

Operators perform their tasks by reaching into the work zone via robotic arms, flexible sleeves and gloves, or half-body suits. Modular isolator units can be strategically positioned to permit loading/unloading of processing equipment required for sterile production.

Because people are the main source of bioburden in clean-room operations, the primary advantage of barrier technology is obvious. However, other advan-

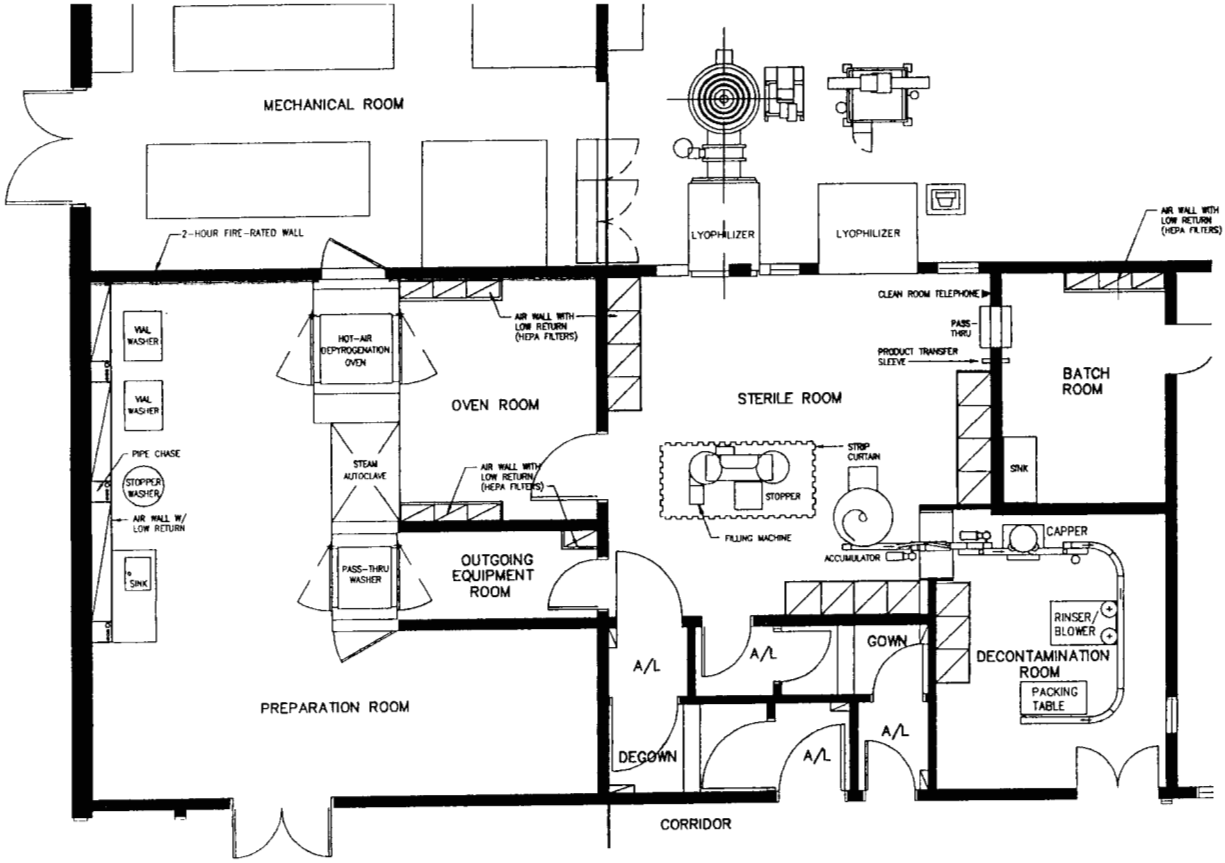

FIG. 5. The sterile area floor plan with key processing equipment and design features included.

tages apply to processing of regular, as well as hazardous sterile products. These include the following:

Maintenance of sterility in event of power interruption
Reduced operating costs (frequent air changes are avoided)
Elimination of gowning costs, including destruction of contaminated gowns
Flexible movement of personnel without need to shower after each work shift
Provision of total barrier between worker and toxic product
Better utilization of facility space

Disadvantages might include:

Difficulty in performing nonautomated steps (loss of tactile sensitivity using heavy gauge gloves)
Weakness of gloves to provide adequate protection for some anticancer compounds
Need to maintain positive pressure within isolator for sterile filling operations (this is dangerous if system is not completely sealed)
Hard to clean all components or surfaces

VII. CONCLUSION

Facilities in which cytotoxic clinical supplies are produced or handled must be designed and engineered to protect workers and the environment. Special HVAC systems featuring computer-balanced room pressure differentials, strategically placed airlocks, extensive training, and complete gowning all help protect facility workers. Terminal HEPA filtration on the facility's exhaust air, neutralization of aqueous effluent before sewering, and proper disposal of organic solvent or solid wastes help protect the external environment. Advances in barrier (isolation) technology may make this approach to containment a viable option when considering facility design.

ACKNOWLEDGMENT

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13

Contract Manufacturing and Packaging of Clinical Trial Supplies

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I. INTRODUCTION

It's 2:00 A.M. You jolt awake. Another nightmare! What was it? The FDA conducting that same Preapproval Inspection over and over again? The Medical Director calling you about the protocol changes she made 6 weeks ago and "didn't think they were that significant?" Your boss asking, "Why haven't you taken any vacation this year?" right after drilling you for neglecting to submit your monthly report during the month you covered for him while he was gone? His boss asking you to "Help me understand why you still need more people" right after he signed a contract for several hundred thousand dollars for contract manufacturing of clinical trial supplies?

Even though many of us in this business probably have a few stories to tell, contracting the manufacture or packaging/labeling of clinical supplies does not have to be a nightmare. This chapter focuses on what you can do to rest easier at night when the possibility of contracting looms ahead. It provides an overview on some of the basics. Why do organizations contract, and what are some of the advantages and disadvantages? What are some of the key steps in defining a project? How does one find, select, audit, and start up a contractor? Why does it take so long to get a signed contract? How does one manage the thing once it is started? What things can go bump in the night? Although an entire book could be dedicated to this subject, this chapter provides some general guidance to make a clinical supplies contracting project if not an enjoyable experience at least a manageable one.

II. WHY CONTRACT CLINICAL SUPPLIES MANUFACTURING AND PACKAGING/LABELING?

An organization may want to contract for several reasons. Perhaps it is short of the personnel or technology required for the project. The drive to reduce costs, evidenced by the many recent mergers/acquisitions in the pharmaceutical industry, may have led the company, like others, to search for other ways to eliminate or reduce fixed costs. Contracting out clinical trial supplies converts the costs into variables and eliminates the need for a set number of people, facilities, and equipment. Or maybe the organization does not want to be tied up for a large but not complex operation. There are both advantages and disadvantages to contracting clinical trial supplies. As with many decisions we make, there is rarely a perfect solution. In wrestling with the decision of whether or not to contract, one must decide which set of problems (or opportunities) to manage. Table 1 shows some of the advantages and disadvantages to consider.

There is much to consider in deciding whether or not to do a project in-house or contract it out. While the list in Table 1 does not include all the con-

TABLE 1 Comparison of Some of the Advantages and Disadvantages of Contracting Versus In-House Production of Clinical Trial Supplies

Advantages	Disadvantages
Keep Inside	
More direct control of the outcome.	May have to delay another "hot" project.
You set priorities on multiple projects.	Technology may need to be acquired/upgraded.
Usually lower cost (your people were going to be on the payroll anyway).	Facility may need to be acquired/upgraded.
Technology transfer process may be easier to manage internally at a later stage.	Could tie up internal capacity for extended periods, especially on large non-complex projects.
Contract Out	
Contractors have exposure to and experience with multiple companies. Can learn from contractors.	Can be more expensive.
Time can be saved if you do not have technology, facility or personnel.	Sometimes NOT a quick turnaround (especially with a high demand technology).
	Will take longer if contractors are not already prequalified.

(*continued*)

TABLE 1 Continued

Advantages	Disadvantages
Contractor could have more experience and better systems in specialized fields.	Resources are needed to manage the contractor (travel, time, audits, establishing contracts, etc.)
May be able to keep a fast track project on track	Differences in how the two companies do business (i.e., cultures) can take some time to work through.
Can avoid capital investment in costly, seldom used technologies and facilities.	Communication can be more cumbersome.
Can apply internal resources to new chemical entities while contractor addresses more repetitive operations.	Can have less control of schedule.
Projects may be completed with turnkey approach (e.g., manufacturing through to distribution).	Lack of clear expectations up front can result in unnecessary rework or lost time.
Can test robustness of process.	

siderations, it does provide an overview of some things to think about when making a decision. Proper planning and adequate resourcing will mitigate many of the disadvantages.

III. TYPICAL CONTRACTING PROCESS FLOW

The ways to approach the task of contracting clinical supply materials may vary. The organization's immediate needs and short timing often dictate the route that is taken. A first experience with contracting will be more likely to succeed if extra time is planned for the process. Once more experience is gained, the process can be completed more expediently. Even more time must be planned if there is a need to conduct contract work in another country.

The contract process flow in Fig. 1 shows an approach to accomplish the goal of obtaining clinical supply product from a contract service organization (CSO). The following is an overview of the process. Later in the chapter, each of the tasks is discussed in more detail.

It is important to obtain enough detail about a project initially to make a decision about whether to contract the project. This needs to be determined as soon as possible because, depending on the scope of the work to be contracted, the coordination, production, and receipt of supplies could take several months. The operations group in the organization should understand their capabilities so that they know which project requirements will trigger the utilization of outside resources. For example, if there is a potential need for an injectable form of the product for a phase I study, and there are no facilities to manufacture sterile products, it will be necessary to begin making plans with a CSO for sterile production of the injectable. If the organization does not have the capability of packaging products in blister cards, the service will need to be outsourced.

Understanding the company's capabilities and the potential project will aid in determining which CSOs have the potential to meet the project needs. To select the most suitable CSO, candidates should be evaluated to determine whether they meet the company's quality, timing, and cost objectives. This qualification process may take several weeks because it involves scheduling, conducting, and reporting audits. Prequalifying contractors before having all the details of a specific project saves overall project time. The prequalification may be limited to good manufacturing practices (GMP) compliance assessment, or it may also include an evaluation of technical and business capability. With qualification completed, the time it takes to schedule, conduct, and report qualification audits can be eliminated from the overall project time. Once you know which CSOs meet compliance, business, and technical capabilities requirements, the remaining factors in selecting a CSO may depend only on the specific project requirements, timing, and cost objectives.

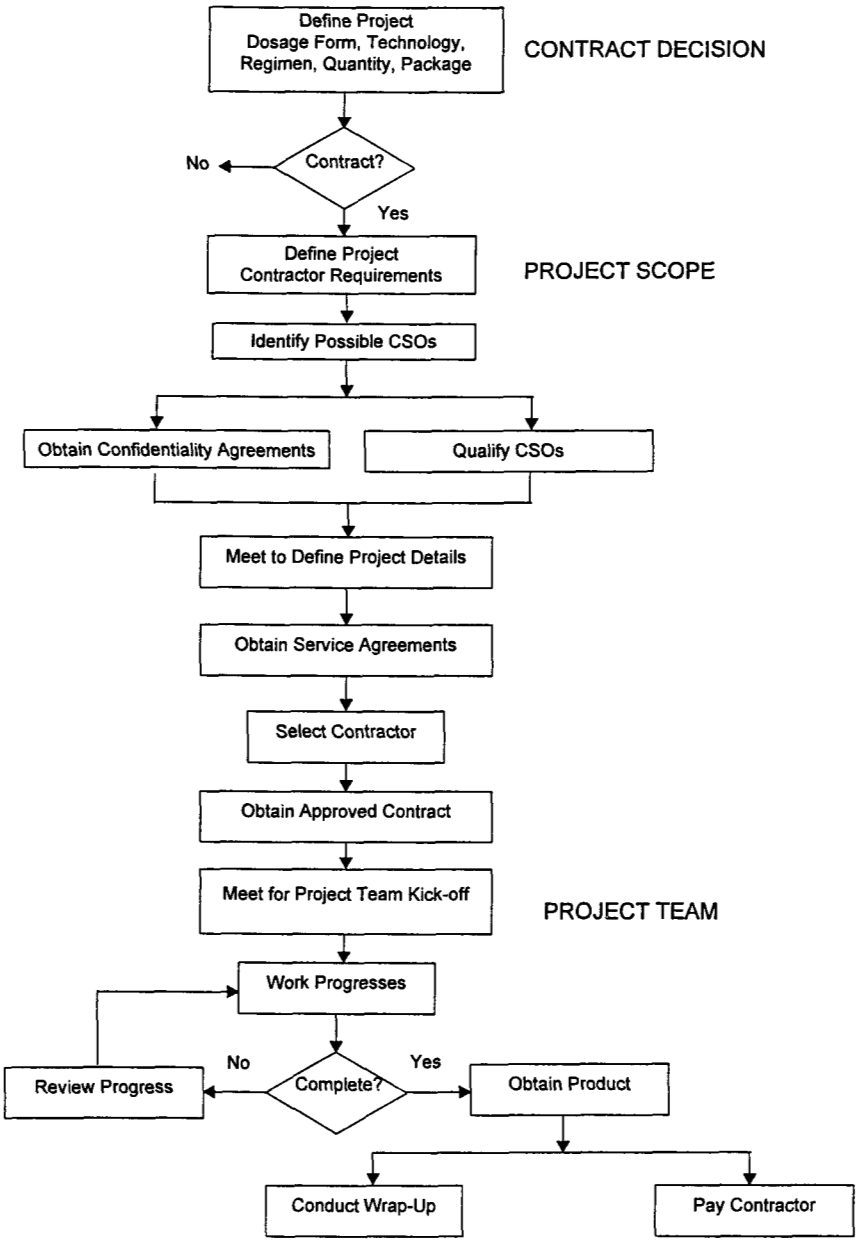


FIG. 1. Flowchart of major activities involved in contracting clinical trial supplies.

Before sharing proprietary information, a confidentiality disclosure agreement (CDA) is advisable to protect the interests of both parties. It says that either party will not share information with a third party without permission of the other party. Signing a CDA may be accomplished before the qualification activities or in parallel with them. Most certainly it must be completed before sharing specific proprietary project information or technology that is unique or patentable.

After the CDA is in place, one should plan to meet face-to-face with the CSO to clearly define the project in more detail. Conveying information via phone call, facsimile, or mail is not a good substitute. Meeting in person provides both parties with an opportunity to begin a relationship for project success. Ideally, the meeting should be attended by key players from both companies. After the companies have built their relationship by working through some projects together, a start-up meeting may not be needed. In either case, joint definition of the success criteria for the project, expectations, responsibilities, and the project schedule will improve the success of the project. This information will be needed for the CSO to prepare accurate service agreements and contracts. Approval of the agreements or contracts is needed by both organizations before commencing work on the project.

After the agreements or contracts are in place, one should meet again with the CSO to address project details. At this meeting, personnel who will manage and conduct the work from both companies should jointly review the project success criteria, review the service agreements or contracts, define team activities, and prepare responsibility charts and timelines. Primary contact persons should be identified at each company to act as liaisons to ensure a strong communications link. Additionally, technical persons at each company should be identified and introduced to ensure that technical information is communicated and interpreted for project success. The ultimate goal of the joint project team is to ensure the project meets the predefined success criteria.

Throughout the course of the project, routine project meetings or conference calls should be held to track progress on the timeline and realign, as necessary. For fast track projects, daily or weekly updates by phone between the CSO and the organization ensure that the project stays on track. This also helps to identify and resolve issues before they become problems.

Finally, after project completion, a wrap-up should be conducted to review the project's success criteria. Were the success criteria met? What went well and what could be done better/different next time to improve efficiency, communication, quality, science, etc.? Documenting this will save time in the future. Plan to reapply the information to the next contracted project.

IV. PROJECT DEFINITION

Have you ever had the "opportunity" to experience the following scenario? You, the person responsible for on-time delivery of quality, packaged and labeled clinical trial materials to the clinical sites, receive a memo dated May 14 that states: "The Medical/Clinical department will be initiating phase II clinical trials on Product XYZ sometime in August. There has been no decision on the dose regimen. A capsule or tablet formulation will be used. Most supplies will be provided in amber glass bottles, but once the European sites are defined, blistered material may be needed. Please be prepared to ship the materials to clinical trial sites by August 1."

Most in the field will probably attest to the fact that this is a rather typical request for clinical supply organizations, except that this example may have provided more time than usual! In general, due dates are established by the Medical/Clinical organization and your job is to make sure you have quality supplies at the sites by the required date. The time is almost always significantly less than what is needed to accomplish the job.

Inevitably, a clinical supply organization's first reaction is that there is no way it can be done. Another way to view this challenge is to consider how the product may help patients once it is on the market. Reducing time in the product development life cycle could save lives or improve the quality of life for someone. From a business perspective, one should consider the dollars of future company revenue to be gained and expenses to be saved for each day that is saved in the development process. These considerations add a new perspective to the importance of working to meet the aggressive time schedules often required of clinical supply organizations.

The bottom line is that a clinical supply organization's normal operations must include fast turnaround of quality supplies. To do this requires a clear definition of what is needed. The following describes at least three ways to help prepare for express service requests.

1. Establish a contact and system for sharing information with the organization that provides requests. Clearly define the details and information needed to accomplish the work and when the information is needed. Keep the requesting group informed of progress.
2. Know the organization's capabilities and the Operation group's limitations; define the circumstance that would necessitate work with a CSO.
3. Identify CSOs that will complement the organization's capabilities and work as partners. Confirm that they will meet the business, technology and quality requirements and respond quickly to requests. The cost of service, although a consideration, should not be the determining factor.

Table 2 depicts some typical information needed at various points in the project. The level of details required progress as one gets further into the process with a CSO. Each project may present different details, and the players involved may affect the progress. After gaining experience working with CSOs, one can develop a guide to aid in the preparation, communication, and execution of future projects. This will help save precious time in the future.

Initially, information is needed to decide whether to contract. Understanding the internal capabilities and limitations is the first step. In Table 2, the first column (Contract Decision) lists examples of what one may want to know to help make decisions. A single item or multiple items may be the determining factor. For example, the facility may not be designed to handle the manufacturing of potent products. Therefore, potent product projects need to be contracted. Or the manufacturing and packaging technology may be available to complete the project, but the resources to deliver the quantity of product required in the time it is needed may be lacking. This list should be reviewed and customized for the company. Define what you need to know to make your decision and convey it to the appropriate groups responsible for providing these project details.

The second column (Project Scope) includes examples of information needed by the CSO to define the scope of the work and to determine potential costs. Although this will vary with the project and the CSO, this list gives some idea of what is needed before contacting a CSO. When requesting a service agreement, jointly define the project success criteria and provide as much information as possible to the CSO. For example, if the product was manufactured previously, copies of production batch records could be provided. Communicate openly about the product history, including successes and failures. If little information is available, an experienced CSO can help explain what is needed to make the project successful. Be clear about what services are expected from the CSO and what they can expect from the company. Changes in the scope after the project has begun may add costs and delays to the project timeline.

The third column (Project Team) lists details that should be addressed by a joint project team. The list should be customized to the specific project at the project kick-off stage. Pay particular attention to these details, clearly communicating them, defining responsibilities for them, and writing them down. The best means of accomplishing this is to have a face-to-face meeting attended by members of both organizations that are responsible for the business, technical, and quality details. Depending on the scope of the work being contracted, attendees may represent formulations development, quality assurance, project management, production and packaging, regulatory, analytical, etc. At the initial meeting, the team should review the service agreement or contract and the

TABLE 2 Different Levels of Detailed Planning Required as Process Progresses. (The flowchart in Figure 1 shows when these levels of detail are appropriate.)

	Contract decision	Project scope	Project team
Manufacturing technology	Manufacturing technology Packaging technology	Specific equipment Batch size Confidentiality agreements Packaging requirements Manufacturing process history Package & study design	Critical process parameter Tooling
Materials	Quantity of product Drug substance safety Package type	Availability of drug substance Definition of excipients Drug substance MSDS	Specifications Test procedures Drug substance & excipient specs Safety precautions & special handling Delivery dates
Schedules	Estimated clinical start date	Expected CSO ship date Expected date of arrival for drug substance, packaging materials, excipients at CSO	Master record approval Material release date Manufacture date QA release date Ship dates

Quality and testing	Identify process for testing	Status of analytical methods validation Required tests	Sampling plans Batch records Test method transfers Cleaning validation tests & documentation
People	Responsible for contractor decision Resources available to complete project	QA release responsibility Internal project management responsibility Testing responsibility Excipient and packaging materials sourcing responsibility Formulation development CSO liaison Analytical support responsibility Label generation/approval responsibility	CSO project management responsibility Person in the plant Communication norms Responsibility chart Communication liaison Technical contacts

success criteria. This team may opt to add additional success criteria. The initial meeting outcome should include identification of personnel who will act as liaisons between the companies to facilitate communications. Additionally, technical persons at each company should be identified and introduced to address technical aspects of the project as a team. Other meeting outcomes include updated success criteria and a project timeline that includes a comprehensive list of all the tasks with responsibilities and completion dates assigned.

If circumstances do not allow a face-to-face meeting, it is still important to achieve the expected outcomes through a conference call attended by the appropriate personnel from both organizations.

Some CSOs may provide a form requesting technical details of the project. This is a tool that could be used during a face-to-face meeting or during a conference call. The form may help to collate technical information from the internal personnel to facilitate communications with the CSO. From the CSO perspective, the document could be an extremely valuable communications tool to ensure the organization's needs are met by them. Table 3 outlines topics typically covered in a CSO Technical Information Form.

TABLE 3 Outline of CSO Technical Information Form

- Product name and strength
- Desired quantity
- Material safety data sheets
- Manufacturing process
- Formulation—Unit formula
- Raw materials
- Raw material specifications
- Material suppliers
- Previous batch history:
  - Batch size(s), process changes and why, study results to determine critical process parameter targets
  - Solid dose forms: bulk density, tap density, particle size, angle of repose, moisture
  - Liquids/semisolids: specific gravity, viscosity, pH
- Recommended equipment and tooling
- Recommended batch scale
- Environmental requirements:
  - e.g., temperature, humidity, light
- Critical process steps
- Target process parameters
- Sampling plans
- Acceptable quality limits
- In-process controls:
  - e.g., LOD, moisture, disintegration, dissolution, particle size, potency, bulk and tap density, appearance, weight variation, hardness, thickness, content uniformity, friability, microbial quality, viscosity, specific gravity, osmolality, pH, particulates
- Clinical study design label details:
  - e.g., open, double blind, language, country
- Study protocol
- Package design
- Package components
- Package component specifications
- Treatment groups
- Number of patients
- Study sites
- Frequency of distribution

V. CONTRACTOR SOURCING AND SELECTION

Sourcing a contractor and qualifying them may take several weeks and, possibly, months. If the cost and time spent up-front is justified, it is best to undertake this process before a contractor is needed. One of the dilemmas faced by clinical supply organizations is that the majority of CSOs support large scale production instead of the smaller scale required for clinical trial supplies. There are a limited number of experienced CSOs for clinical production, especially for small volume parenteral products.

A. Sourcing

How does one find a CSO? First, one must define what is needed from a technological standpoint, timing, etc. (see Table 2, Column 1: Contract Decision, and Column 2: Project Scope). Know what equipment or process steps are required. Have a general idea of the batch scale that is needed before calling since many organizations may only be large scale producers.

Call business associates at other companies. Contact some of the persons listed in the participants list from a conference or seminar attended where pharmaceutical development or clinical supply personnel were in attendance. Other good sources are pharmaceutical trade journals and pharmaceutical associations such as the Drug Information Association. Seek another client's viewpoint about the capabilities of the CSO and how well their needs were met. This will help determine whether further contact is appropriate. If a CSO cannot meet the organization's needs, ask whether these are others that might be potentials.

An important factor to consider when identifying a potential CSO is the location. Logistics of shipping materials, documents, and so on can be more cumbersome when working internationally. When shipment of product from one country to another is anticipated, it is important to involve a regulatory expert early in the process to define the import/export requirements of the project. Usually, these can be addressed with the proper documentation and planning, but this will add time to the project.

B. Qualifying

Once the CSO is defined, audit the facility before making a commitment to utilize their service. In general, there are three areas to evaluate:

- Ability to meet business, technical, and quality requirements
- GMP compliance
- Confidentiality

These evaluations may be done in numerous ways; however, it is most effective to have a small team (about three to four people) visit the facility. This

reduces the amount of time demanded of the CSO and also provides the opportunity for key project people to evaluate, discuss, and identify the adequacy of the CSO. Representatives should include a person qualified to conduct a Quality Assurance (QA) compliance audit, a technical person who knows process and equipment requirements, and the person who will be responsible for the business and/or technical coordination between the two organizations.

1. The Current Good Manufacturing Practices Compliance Audit

The QA auditor will evaluate the CSO's ability to meet GMP regulations. The auditor may review past FDA citations (FD483s) and the CSO's responses to them. Systems and Standard Operating Procedures may be audited to determine whether the CSO knows what it is expected to do and whether it can do it. An important aspect to evaluate at the CSO is its cleaning validation/verification procedures because it works with multiple products and its equipment is probably nondedicated. Before leaving the CSO, the auditor should provide direct feedback to the CSO's QA and Operations management to describe findings and request any corrective actions, if necessary. Depending on the findings, the auditor may find it acceptable to proceed with the work and request that corrective actions be taken in parallel with project preparation activities. Most often, allow the CSO about 30 days to respond to a written audit. A follow-up audit may be scheduled to assess the compliance specifically on the product before, during, or after production is initiated. It is a good practice to check whether corrective findings were addressed as promised by the CSO. Because organizational climates change, QA audits should be conducted periodically. Many companies conduct them annually.

2. The Technical Audit

The technical evaluator should determine, through questioning and observation, whether the CSO has the personnel with appropriate technical expertise to perform the desired work. *Curriculum Vitae* and training documentation of specific individuals should be reviewed. Also, it should be determined that the equipment to be used is the appropriate design and scale for the intended batch size and that appropriate data will be collected at critical process steps to substantiate future process modifications. This evaluation may be conducted to get a general overview; however, if a specific project is planned, it is better to do an in-depth evaluation.

It is important to consider the specific project that you may contract during the technical evaluation. If the product is developed at the same company that will make the clinical trial supplies, evaluate their technology transfer process. How is information transferred internally to ensure project success? Will the clinical batch sizes be a different scale than what was done in development? Is the equipment different? If there are scale and equipment differ-

ences, will an experimental batch be made to assess the process before making the clinical supply batch? If not, what controls will be in place to ensure that the clinical batch is made successfully? What role will the formulation developer play in the initial batch production? Similarly, these questions need to be answered if the formulation development was accomplished at the company or at a third party company. Do not assume that because the product could be made at one site at a similar scale and with a similar process, that it will be made successfully at the contractor site the first time. At the clinical supply stage, when processes are not fully developed or validated, unknown factors can result in a failure with the initial technology transfer. Attention to processing details and the critical process parameters during the technology transfer can reduce this level of risk.

The technical evaluator and the QA auditor may recommend that an experimental batch be made before GMP production or other measures that will ensure compliance with GMPs and the March 1991 FDA Guideline on the Preparation of Investigational New Drug Products. This document reiterates the requirement that clinical supplies be manufactured in compliance with current good manufacturing processes (cGMPs). The guideline discusses the need for process validation of clinical drug products intended for use in animals or humans. Process validation, at this stage of drug development, may be limited. For example, on a batch basis, it may be possible to collect in-process control and product test data that proves the product meets quality and specification requirements.

An experimental batch will provide the opportunity to assess the process at a new site (at the same scale and in the same equipment) to identify process parameters for the GMP batch. If this is not feasible, the CSO will need as much technical detail as possible about previously made batches (e.g., for blends: bulk and tap density, angle of repose, blending time, blend sampling techniques, typical content uniformity, and assay data). The reason for sharing this level of detail is to aid in a successful technology transfer. Some companies may recommend that each clinical supply batch be prepared under a process validation plan. A protocol is prepared for each clinical batch, which is the result of a prospective evaluation of the process. Critical parameters and acceptable quality levels are predefined and a sampling and testing plan outlined. This protocol is followed in addition to the batch record. The samples generally are more than required for release testing of the clinical batch. The test results are collated and evaluated for trends and to note differences among clinical batches made throughout the product's development stages. It is extremely important that the CSO and client work together as partners for a successful technology transfer. The QA and technical auditor set the stage for the project success through their evaluations and subsequent recommendations.

3. The Business Audit

When evaluating the business aspects, consider the role the CSO plays in the overall industry. Is it well established? What is the size of the company? What impact might its size play on its ability to meet the company's needs? Is the CSO a "start-up" company, or is it experienced? How much business does this CSO generally have? What is their process for generating service estimates and contracts? What are typical turnaround times for CDAs, service estimates, and contracts? While these issues may not be the primary deciding factors in the selection process, they should be considered.

Find out how the CSO manages projects. If possible, meet with the personnel directly responsible for managing the work such as production, laboratory, quality assurance, and regulatory and project managers. Determine their mechanism for defining priorities and ensuring that projects (similar to the Company's) are managed so that success criteria are met according to plan. Ask how they communicate internally and how they plan to communicate about project progress.

Last, but most important for some organizations, is the level of confidentiality that is displayed by the organization. Because of the proprietary nature of Research and Development (R&D) products, this is critical to many organizations. During an on-site visit to the CSO, questions should be asked to assess how confidentiality is protected. One of the best methods of evaluating is to observe the CSO's practices while on site. Does the company display information regarding other clients? Are batch records secured as they progress through the manufacturing process, or are they left on desks or in process areas that are readily available for visitors to see? Are client names posted on processing room doors in full view of visitors? Are other client names being used in the hallways, offices, and other common areas? Be alert for breaches of confidentiality during the audit. Take this into consideration when making a selection.

After evaluating GMP compliance, technical expertise, technology transfer functions, business aspects, and confidentiality norms, meet with the CSO key personnel to provide feedback. Review the positive findings and note findings that may not be desirable. Take into consideration that the CSO has its own culture, procedures, and methods for complying with cGMPs. Do not impose specific procedures onto the CSO unless there is adequate justification from a compliance or business standpoint. Requiring procedures that are atypical to the CSO norms may lead to unnecessary risks. Let the CSO utilize its own systems and procedures wherever possible; however, now is the time to let them know about valid recommendations for improvement. This meeting should include opportunity for discussion. In the overall assessment and selection process, determine the receptiveness, ethics, and responsiveness of the CSO meet-

ing participants. Discuss follow-up actions. Plan to provide the CSO with a written audit report of the findings. If a written response is requested, discuss expectations and delivery times before ending this meeting. After this process is completed, a comparison may be made with other CSOs, or an estimate of the costs of services may be obtained to help with the decision-making process.

VI. CONTRACT PREPARATION

To obtain an estimate (contract), sufficient details must be provided to the CSO such as described under Project Scope in Table 2. A face-to-face meeting is the best method for communicating and subsequently reaching an agreement on success criteria and the service to be provided by the CSO. This meeting may take place during the qualification stage or after the CSO has been qualified and selected. Plan it as soon as possible. Ask that key personnel from the CSO attend and bring key personnel from the organization.

A joint agenda should be prepared before the first meeting. Either organization may initiate it. It is important that both organizations provide input and it must be distributed to meeting attendees before the meeting. Each attendee should be prepared to address the agenda items. This will make the meeting more productive. A typical agenda (with some added explanations) is as follows:

- Introductions (Identify role on project team)
- Client describes scope of work required
- Discussion to clarify understanding of requirements
- CSO describes specific services that can be provided
- CSO/Client agree on project scope and general responsibilities
- CSO/Client define project Success Criteria
- CSO/Client discuss and agree on estimate process, timing, approval, etc.

If it is not possible to have a face-to-face meeting, a conference call should be held to achieve the same goals as described previously.

Each CSO will have its own style and format for the contract or service estimate. Basically, it will outline the task the CSO is to undertake with a description of the service, the cost of the service, the responsibilities expected of the client and CSO, and statements pertaining to legal terms and conditions including payments and legal liabilities. With the information obtained at the initial CSO/client meeting, most of the contract can be written. The legal terms and conditions usually are reviewed by attorneys representing the parties involved to gain agreement on their respective legal rights and obligations. The first time companies work together, getting agreement between the two may take some time. The best way to reduce this time is to have the attorneys discuss the differences and work out agreeable terms. This approach saves time.

To pave the way for faster turnaround on future contracts, consider having the legal issues addressed in a contract that may be used for any project. A clause in the agreement can prompt a review of the legal terms to ensure they are updated periodically. Project-specific terms, responsibilities, details, and costs may be in a separate document that is generated for a particular project once the details are known. If this method is chosen, both parties' attorneys must agree to it at the outset. Once established, it should save the time of having the legal terms revisited each time. After qualification is completed and the service agreement or contract is received, all the data necessary to select the CSO should be available.

VII. MANAGING CONTRACTED PROJECTS

A. The CSO/Client Project Team

This section describes how to successfully communicate and manage projects after the decision is made to hire a CSO. A face-to-face meeting to kick-off the project is recommended. Those personnel at the company and the CSO's internal project team who will carry out the details or the project should be present. The following list is an example agenda to use for this meeting:

- Review the signed contract and success criteria.
- CSO/Client revise success criteria, if necessary.
- Develop the Responsibility Chart by defining the organization or person responsible for each action and the date for task completion.
- Prepare a Project Timeline.
- Define the communication expectations and norms: e.g., frequency and location of meetings; who will get copied on the CSO/Client project team meeting minutes and receive copies of the tracking tools.
- Identify the project leaders and technical contacts.
- Plan the next meeting.

This agenda includes a thorough review of the service estimate and/or contract and the development of some tools that will be helpful for communicating project details and tracking progress over its life. Although all these tools may not be necessary for every project, it is recommended that an effort be made to utilize some of them. During the meeting, the team reviews the success criteria by asking, "How will we know when we have successfully completed this project to the satisfaction of both the CSO and the contracting company?" The answers are defined jointly and agreed to, the project requirements are discussed, and a responsibility chart is developed with specific project details outlining who is responsible for doing them and when they will be done. Finally, the team may put together a Gantt chart or another type of timeline to show the overall project timing and activities required to complete it. The team

may decide how much detail to include in these charts. They may even be combined into one, using the Gantt chart format with responsibilities assigned to each activity. The following lists are examples of project requirements and success criteria. Table 4 shows a responsibility chart, and Fig. 2 represents an example of a timeline.

Requirements for Project XYZ:

1. One batch of Product XYZ, 10 mg capsules, will be manufactured to yield at least 30,000 capsules.
2. The product will be packaged in appropriate sized HDPE bottles with Child Resistant Closures at 106 units per bottle.
3. 114 bottles of 106 units will be labeled according to Protocol 102586D.XYZ for an open labeled clinical study.
4. 120 additional bottles will be labeled according to the Stability Protocol #12376 for a stability study.
5. The CSO will order magnesium stearate and talc and test according to compendial specifications.
6. Identity tests will be conducted by the CSO for all other materials and package components which will be supplied by the client with Certificates of Analysis.
7. Analytical testing of the packaged product will be conducted.
8. A Cleaning Method Development Protocol will be written, approved and initiated to define cleaning methods specific to Product XYZ.

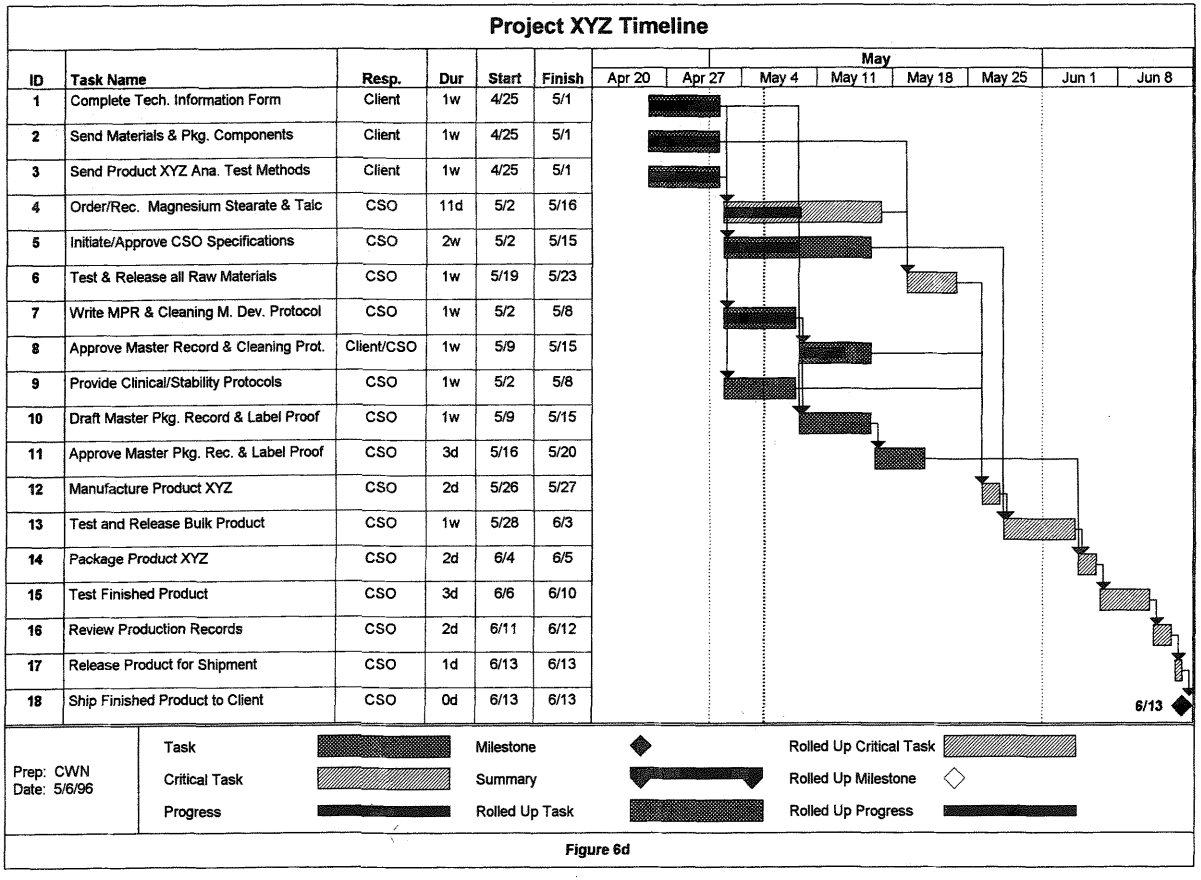
Success Criteria for Project XYZ:

1. Project XYZ meets cGMP, CSO and Client quality standards.
2. Product XYZ is delivered to the Client on time.
3. Communication takes place at appropriate intervals and is shared with appropriate personnel.
4. Action steps defined in the Responsibility Chart take place on time.
5. Final project costs are within the quoted amounts.

At this first meeting, it is important to identify the project leaders and key technical contacts for each organization. Also, the team must define the communication norms. Define who will contact whom for what information and when that contact will be made. Much of this will be project dependent. It is critical that the team set up routine meetings either in person or by phone. Weekly updates are recommended, unless the project does not require them that often. Daily communications may be needed at specific project milestones or for fast-track projects. Technical personnel should know who to contact in their respective organizations to streamline communications. All communications between organizations should be documented and forwarded to the respective project leaders to keep them informed of all activities and communications taking place.

TABLE 4 Responsibility Chart for Project XYZ Illustrating One Way to Track and Communicate Action Items, Responsibilities, Due Dates, and Status of Projects as of 5/6

Action	Responsible	Due	Status
Complete technical information form	Client	5/1	Completed 5/1
Send materials and package components	Client	5/1	Completed 5/1
Send product XYZ analytical test methods	Client	5/1	Completed 5/1
Order magnesium stearate and talc	CSO	5/2	Completed 5/2
Initiate/approve CSO specifications	CSO	5/15	In Process
Receive magnesium stearate	CSO	5/16	Received 5/6
Receive talc	CSO	5/16	Due in on 5/10
Test and release all raw materials	CSO	5/23	Awaiting specs
Write master production record	CSO	5/8	To Client 5/6
Write cleaning method development protocol	CSO	5/8	To Client 5/6
Approve master record and the cleaning method development protocol	Client/CSO	5/15	In Process
Provide clinical protocol	Client	5/8	
Provide stability protocol	Client	5/8	
Draft master packaging record	CSO	5/15	
Draft label proof	CSO	5/15	
Approve master packaging record and label proof	Client/CSO	5/20	
Manufacture product XYZ	CSO	5/21	
Test and release bulk product	CSO	6/3	
Package product XYZ	CSO	6/5	
Test finished product	CSO	6/10	
Review production records	CSO	6/12	
Release finished product	CSO	6/13	
Ship finished product to client	CSO	6/13	



ID	Task Name	Resp.	Dur	Start	Finish
1	Complete Tech. Information Form	Client	1w	4/25	5/1
2	Send Materials & Pkg. Components	Client	1w	4/25	5/1
3	Send Product XYZ Ana. Test Methods	Client	1w	4/25	5/1
4	Order/Rec. Magnesium Stearate & Talc	CSO	11d	5/2	5/16
5	Initiate/Approve CSO Specifications	CSO	2w	5/2	5/15
6	Test & Release all Raw Materials	CSO	1w	5/19	5/23
7	Write MPR & Cleaning M. Dev. Protocol	CSO	1w	5/2	5/8
8	Approve Master Record & Cleaning Prot.	Client/CSO	1w	5/9	5/15
9	Provide Clinical/Stability Protocols	CSO	1w	5/2	5/8
10	Draft Master Pkg. Record & Label Proof	CSO	1w	5/9	5/15
11	Approve Master Pkg. Rec. & Label Proof	CSO	3d	5/16	5/20
12	Manufacture Product XYZ	CSO	2d	5/26	5/27
13	Test and Release Bulk Product	CSO	1w	5/28	6/3
14	Package Product XYZ	CSO	2d	6/4	6/5
15	Test Finished Product	CSO	3d	6/6	6/10
16	Review Production Records	CSO	2d	6/11	6/12
17	Release Product for Shipment	CSO	1d	6/13	6/13
18	Ship Finished Product to Client	CSO	0d	6/13	6/13

FIG. 2. Another tool for project tracking that focuses on the timing for completion of action items. The timeline also shows which actions depend on others.

The meeting minutes should be documented, and all project management tools developed should be drafted and shared. Meeting minutes and the tools should be issued only after both parties have agreed to their contents.

B. The Internal Project Team

Ideally, an internal project team should be established in the respective organizations. Most important, there should be one at the CSO who is expected to meet the success criteria for the project. This group may be the same team that meets routinely with the client, or it may be an expanded team. The team members should represent all the functions of the CSO that will provide a service to achieve the project goals. This team utilizes the tools developed by the CSO/client team as its guide to achieve and track progress.

C. The Preproduction Tasks and "Person-in-the-Plant"

A contact should be identified at the client site to work directly with the CSO clinical supply organization for the preproduction tasks that must be accomplished in the manufacturing area. Efficient and accurate coordination of logistics can help to minimize the overall time in getting ready for production. These tasks include the sourcing and testing of raw materials and the preparation and approval of the master production and packaging records.

To aid in the technology transfer process, one may choose to be present at the CSO during the first few manufacturing runs. Ideally this "person-in-the-plant" should be an experienced scientist who is technically familiar with the product being made. This provides production operators and managers the opportunity for a one-to-one exchange of information throughout the manufacturing or packaging process. The "person-in-the-plant" may observe systems and procedures, and the CSO operations personnel can have an opportunity to ask questions to gain more knowledge about the process from an experienced scientist.

VIII. PROJECT FOLLOW-UP EVALUATION

After the products are made and delivered by the CSO, there is still one last step to take. This is the time to evaluate how things went with the project and to capture the problems and successes encountered so that information may be applied to future projects. Continued improvement should be an ongoing goal with contracted projects. The following scenario is an example of a typical follow-up evaluation.

First, you and the CSO should agree that this is an important step in the overall process. As the project proceeds, immediate feedback on issues and successes should take place. However, at project completion, each group should separately meet with respective internal project teams or key individuals who worked on the project to collate information that will be shared with the other party. Some questions to consider include:

- Were we successful in meeting the project timeline and success criteria? If not, what could we do the next time to be successful?
- Did we jointly satisfy the actions outlined in the Responsibility Chart? If not, what can we do differently next time?
- Did we communicate effectively? Did the other party communicate effectively with us?
- Are there process changes that we would recommend for the next batch or set of products to be made?
- Are there ways to save costs or time?

After summarizing this information, hold a meeting with the CSO either by phone or face-to-face. Provide each other with the feedback that has been obtained. Each party should listen attentively and seek to understand the input provided by the other to make this meeting successful. If the meeting is conducted in a positive manner, synergistic solutions can be realized that will benefit both the CSO and the organization. Document the decisions made and the suggestions for improvement. Then make sure this information is used during the start-up phase of a new project.

IX. INTERNATIONAL CONSIDERATIONS

Given the current globalization efforts taking place in the industry, a few words about contracting internationally seem appropriate. As mentioned earlier, the process may take longer because of the overall logistics; however, as with contracting domestically, planning and early project communication will facilitate the project overall.

Communication is an important factor when doing business internationally. Even though English is usually a common language, the differences in cultures result in differences in what we say, how we say it, and how we respond to what is being said. The paradigms of individuals also enter into the communication equation. Because of differing regulatory requirements, the knowledge or understanding of what is required may add to the complexity of defining project requirements and communicating project needs. In general, be attentive to these differences and the fact that misunderstandings can result.

One way to aid communication is to convey information in writing whenever possible. Important decisions, project commitments, meeting notes, and other project planning tools should be written. Hold face-to-face meetings, phone calls, and video or phone conferences frequently to maintain the flow of communications. By prearranging an agreeable time for phone calls, time difference hurdles can be overcome. When communicating verbally, seek feedback from the other parties involved to be assured of their understanding. Avoid asking the question, "Do you understand?" It is better to have them describe to you what they understand. When necessary, involve a translator to facilitate communications.

The other two important considerations when working internationally are regulatory requirements and logistics. From a regulatory perspective, one needs to know the requirements for the country in which the product will be manufactured or packaged and the requirements of the country or countries where the clinical trials will be conducted. For example, what specifications must the materials be tested against? What finished product tests and samples are required? What are the labeling requirements? The challenge is to meet the regulations in all applicable countries. These regulations affect logistics of shipping drug substance and product across international boundaries.

As with most first-time experiences, expect the process to take longer and plan ahead. By following the guidelines provided in this chapter, the contracting of projects internationally can be accomplished successfully. Involve the regulatory group and, if possible, establish a reliable regulatory contact in the countries where you may want to contract or conduct clinical studies. This will aid in meeting the regulatory and logistics challenges. Remember to maintain focus on good communications.

X. SUMMARY

This chapter presented the basics of contracting of clinical trial supplies, from things to consider, advantages and disadvantages, the process flow, defining the project, CSO sourcing and selection, project management, and tips on managing the details. All of these items and personal experience and perseverance will be needed to effectively manage the clinical trial supplies contract. Although the choice to contract may not be optional, thinking through the process and establishing systems to effectively manage the contractor interface can make the outcome, if not easier, at least predictable and manageable. It should also help you sleep better at night should you find yourself in a contract clinical supplies situation. Although the process is a lot of work, it doesn't need to be a nightmare!

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Overseas Trials

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I. OVERVIEW

For expeditious registration of drugs on a worldwide basis, it is important to perform clinical trials in a variety of countries. On the other hand, it is impractical to manufacture, package, and release clinical trial supplies in every country in which clinical studies are conducted. As a result, clinical trial drugs are routinely exported from one country to another. In most countries, import or export is straightforward provided that the supplies are not controlled substances and are being used for investigational use only. However, export of clinical trial supplies or investigational drug substances from the United States is an exception.

Regulations on the export of investigational or biological drugs from the United States differ depending on the country to which the materials are shipped. The FDA Export Reform and Enhancement Act of 1996 states that no prior FDA approval is required for shipment of investigational products to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the European Union or the European Free Trade Association Member States (Austria, Belgium, Denmark, Iceland, Germany, Greece, Finland, France, Ireland,

Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, and the United Kingdom). The Act states that the exporter must notify the FDA within 90 days of shipment indicating the name of the product and its strength. However in addition to this information, the FDA has requested that the exporter voluntarily provide (a) quantity shipped, (b) consignee name and address, and (c) indication(s) for which the product is being investigated. The Act has greatly simplified the export of investigational products to the 24 listed countries. However, the interpretation of certain aspects of the Act, particularly the jurisdiction of the FDA in the transshipment of investigation products from listed to unlisted countries, remains to be clarified.

All exports of investigational drugs or biologicals to other than the 24 listed countries must be authorized by the FDA. The authorization for export can be obtained either via an Investigation New Drug (IND) submission or through a request for export to the International Affairs Staff of the Office of Health Affairs. If a company is seeking export of an investigational drug outside of an IND, it must provide information to satisfy the FDA that the drug is appropriate for the proposed investigational use in humans, that the drug is for investigational purposes only and that the drug may be legally used by the consignee in the importing country for the proposed investigational use. Until recently, the FDA has insisted that the requester provide a letter from the Ministry of Health of the importing country stating that the consignee may legally use the product for the proposed investigation in that country. For many countries, it was difficult to obtain an appropriate letter from the health authority in a timely fashion. As a result, in 1992, the FDA introduced an alternate submission procedure to expedite the export approval process. With the new process, in lieu of a letter from the foreign health authority, a company may choose to notify the Ministry of Health in writing stating its intention to conduct a clinical trial in that country, sending a copy of the notification letter to the FDA. If the foreign health authority does not object to the proposed export within 30 days, the FDA will presume that there are no official objections. In addition to the notification letter, the company must also submit a certification statement signed by the firm's responsible authority and US legal counsel stating that, based on a review of the country's laws and regulations, the drug can be legally used in the importing country for the stated purposes. The various options for exporting investigational drugs from the US to unlisted countries have been reviewed by Nightingale and Limoli of the FDA's Office of Health Affairs (1).

The supply of clinical trial drugs on a worldwide basis is complicated by differences in language, medical practice and regulations. Despite efforts by the U.S., European, and Japanese regulatory authorities to harmonize standards and requirements, significant differences in regulations and guidelines for clinical trial drugs still remain. This chapter examines the current situation in three

countries/regions: Europe, Australia, and Japan. Although there are undoubtedly idiosyncratic practices in other countries, these three areas represent a good cross-section of requirements for clinical trial drugs outside the United States.

II. CLINICAL TRIALS IN EUROPE

A. General Comments

The sheer diversity and number of countries in Europe mean that there are numerous challenges related to the conduct of multicenter clinical trials in this region and in particular to the provision of clinical supplies. Each country has its own legislation, which varies enormously.

As with regulations concerning marketed products, there have been efforts by the European Union (EU), formerly the European Community (EC), and the Nordic countries to harmonize the different regulations pertaining to investigational products. The Nordic Guidelines for Clinical Trials of Drugs adopted in 1980 and revised in 1983 (2), and the French Bonnes Pratiques Cliniques issued in 1987 (3) paved the way for the EU Guide for Good Manufacturing Practice for Investigational Medicinal Products, which came into force in July 1993 and was revised in 1997 (4). As of January 1997, the membership of the EU stands at 15 countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, United Kingdom (U.K.), and it is anticipated that this membership will continue to expand. To make eventual membership of the EU by any Nordic country easier, The Nordic Council on Medicines (Nordiska Lakemedelsnamnden (NLN)), when developing and revising guidelines, have taken steps to be consistent with existing EU guidelines. In 1989, the NLN ceased it activity on the preparation of guidelines with a view to adopting the EU guidelines. Currently, Norway and Iceland are the only Nordic countries that are not members of the EU. Because the EU is set to assume greater importance for the countries of Europe, the evolution of the EU Guide for Good Manufacturing Practice for Investigational Medicinal Products (4) is considered in greater detail.

In 1991, a Directive (91/356/EEC) laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products was adopted by the Commission of the European Communities (5). More detailed guidelines in accordance with these principles were published in the EU Guide to Good Manufacturing Practice (6). Included in the Commission Directive was a "whereas" statement, stating that Member States may require compliance with the principles of GMP during the manufacture of products intended for use in clinical trials. However, an EU Discussion Paper issued in January 1991 (7) suggested that it was illogical for investigational products not to be subject to

the same controls that would apply to the formulations of which they are the prototypes. Most Member States appeared to be in agreement with this concept. Nevertheless, it was recognized that the manufacture and supply of investigational products are different from the procedures undertaken for marketed products, and that the existing EU Guide did not fully meet the specific requirements of clinical trials. Therefore, it was agreed to prepare an Annex to the EU Guide to Good Manufacturing Practice entitled Good Manufacturing Practice for Investigational Medicinal Products (4). This document became effective in July 1993 (revised in July 1997) and is intended to allow those Member States instituting controls voluntarily, and manufacturers of investigational products, to have a common reference point to enable common standards to evolve in all Member States.

The Annex specifically addresses practices that may be different for investigational products. It recognizes that during development, products are often manufactured as small batches, not always under a set routine, and that there may not be complete characterization of the product, particularly in the early stages. Also, the packaging operations are very different from those utilized during production of marketed products because of the frequent need to produce blinded supplies. An EU Guide for Good Clinical Practice for Trials on Medicinal Products (8) was already in existence, but some areas such as ordering, shipping to investigators, return, and disposal of unused clinical supplies were not satisfactorily covered by either this Guide or the Guide to Good Manufacturing Practice (6). The Annex is not legally binding, and, at present, medicinal products intended for research and development trials are not subject either to marketing or manufacturing European Union legislation. However, individual Member States may have their own local legislation that does encompass investigational products.

B. Regulatory Requirements

As in the United States, major European countries require prior approval of a clinical trial application by the regulatory authority before clinical trials can be performed. There have been significant efforts throughout Europe to harmonize the requirements for the regulation of medicines at the marketing authorization stage. However, there is as yet no harmonization of the requirements for the regulation of medicines at the clinical trial stage. Each country has its own differing requirements and procedures for clinical trial license applications. The procedure in the United Kingdom has changed over the years but is worthy of consideration, as this is the approach that other European countries appear to be adopting. In the 1968 Medicines Act (9) a Clinical Trial Certificate (CTC) was established. Applications for CTCs are made to the licensing authority in the same way as are applications for product licenses. A CTC

application involves full and detailed documentation of the studies and the clinical supplies, which in turn is reviewed fully by the Medicines Control Agency (MCA). The volume of data submitted means that the review process can be lengthy. This led to a reluctance by study sponsors to perform clinical studies in the United Kingdom. The procedure was revised in 1981, when a Clinical Trials Exemption (CTX) scheme was introduced. This is now the principal route by which pharmaceutical companies obtain approval to conduct clinical trials in the United Kingdom. The data requirements are exactly the same as for the CTC, but the data are presented in a summary format. Approval, as with the U.S. IND, is based on a negative vetting procedure. The licensing authority has 35 days (plus an additional 28 days if required) in which to consider and object to the notification. Even if the authority does not respond in this time period, the clinical studies may be initiated. If the licensing authority refuses the CTX, there is no right to appeal, and an application for a CTC must be progressed. However, if the review procedure is successful, its speed compared to the CTC scheme, means that a considerable saving in time can be achieved between application to the regulatory authority and start of the clinical study.

The following information about the clinical supplies is required in a CTX or CTC application:

- Name and address of place where product is manufactured
- Storage site
- Importer
- Name of person releasing clinical material for use in patients and where Quality Control (QC) is performed
- Labeling and packaging details
- Manufacturing details of active substance
- Controls on starting materials
- Controls on finished product
- Development pharmaceutics
- Manufacturing process
- Stability data

Similar information, in differing degrees of detail, is required in applications for licenses in other countries. Switzerland is unusual compared to most of the major European countries in that there is no requirement to obtain a license before performing clinical studies. However, since January 1995, approval by an Ethical Committee has been required for the first time (10), and the Swiss Health Authority must be notified of each study. In other countries, such as Germany, preclinical data must be deposited with the Bundesgesundheitsamt (BGA), but they are generally not reviewed. There is no requirement to provide any chemistry or pharmacy data to the BGA. However the 5th Amendment to the German Drug Law passed in 1994 and effective from Au-

gust 1995 includes more stringent requirements for clinical trial applications in Germany, mainly concerned with Ethics Committee approval and labeling of clinical trials products (11).

In some countries, notably Hungary and Italy, it is necessary to submit samples of each of the clinical trial dosage forms with the clinical trial applications. For other countries, such as Spain, samples may be requested by the authority subsequent to the submission.

In those countries where volunteer studies are permitted, the same regulations controlling the conduct of clinical studies on patients apply to the volunteer studies. The one exception is the United Kingdom where, providing there is Ethical Committee approval, it is permitted to perform phase I clinical studies in healthy volunteers without preparing, submitting, and obtaining approval for a CTC or CTX. The UK Medicines Commission Annual Report in 1984 (12) justified this position by stating that, 'The proper conduct of studies of this kind depends on self-regulation by the medical profession through the use of Ethical Committees." The Commission concluded that the best safeguards lay in effective self-regulation by the profession, rather than in any legislative changes. From the perspective of a pharmaceutical company, this means it is possible to initiate phase I studies in the United Kingdom before these studies could be initiated in other European countries where prior approval must be granted. With the ever increasing drive to shorten the time to market, this can represent a significant advantage.

C. Bulk Manufacturing

1. Good Manufacturing Practice and Inspections

The Annex to the EU Guide (4) recognizes that validated manufacturing procedures may not always be available during the development phase. Therefore, it is difficult to know in advance what the critical parameters are and what in-process controls are necessary to control these parameters. Consequently, it is deemed acceptable to deduce the critical parameters and institute in-process controls based on prior experience with development formulae and processes, revising these as further production experience is gained. In such circumstances, it may be appropriate to increase the level of in-process and quality control testing. Because the quality of the finished product is influenced by the starting materials, specifications for both active and nonactive ingredients should be defined and periodically reassessed.

One area that the Annex to the EU Guide to GMP (4) recognizes as being even more important for investigational products than for marketed products is cleaning procedures. Because knowledge of the toxicity of the investigational product may be incomplete, it is critical that cleaning procedures are shown to adequately remove residual material from processing equipment.

In the United Kingdom, there is at present no legal requirement for manufacture of clinical trial material to comply with GMP standards, or for inspections of manufacturing facilities. A voluntary inspection scheme for those companies that wish to ensure that their facilities comply with the Annex to the EU Guide to GMP (4) has been suggested by the MCA in the UK and may be instigated in the future. In France, GMP inspections of clinical trials manufacturing facilities are performed routinely by the Health Ministry's pharmacist inspectors. The French legislation on the Protection of Persons undergoing Biomedical Research (13) includes a specific provision on clinical trials, stating that, because these are all considered as medicines (even phase I supplies and placebo), they must be manufactured to GMP.

2. Formulation Development

As with dosage forms developed for marketing, it is desirable to develop a clinical trial dosage form with universal acceptability throughout all the countries in which studies are to be performed. However, as with commercial dosage forms, clinical trial formulations are subject to the same constraints concerning choice of acceptable excipients, particularly preservatives and colors. Europe requires that preservatives, dyes, and pigments are identified in formulations.

Identifying a universally acceptable coloring matter is particularly difficult. In 1977, the EU issued a Directive (14) relating to the coloring matters that may be added to medicinal products. This Directive recognized that coloring matters authorized for use in foodstuffs intended for human consumption should also be permitted for use in medicinal products. A revised Council Directive on colors for use in foodstuffs was approved in June 1994 (15). This list determines the coloring matters that may be permitted in medicinal products. As with much of the other legislation, disparities in local legislation further restrict the coloring matters that have widespread acceptability throughout the EU, far less throughout Europe. Some member states of the EU apply the rule laid down for foodstuffs to medicinal products, whereas others maintain separate lists of authorized coloring matters for medicinal products distinct from those acceptable for foodstuffs.

3. Comparators

Supplies of investigational materials for European clinical studies become most complex when the studies incorporate a comparator arm. Because studies at this stage are often multicenter, it would be advantageous if the same comparator could be used in all countries. Unfortunately, this is seldom possible, as the drugs available in one country for a particular indication may be different to drugs available in another. Even when the same drugs are available, the gold standard treatment may be different among countries, or the registered doses

of the drug may be different. Although some countries will permit nonregistered drugs to be used as comparators in clinical studies (it is not permissible in Italy), this approach may not be appropriate. Generally, the regulatory authority will wish to see data comparing the new chemical entity with the gold standard therapy currently available in that country to assess the relative benefits of the new treatment over existing therapy. The Nordic countries, in particular, require a justification for why the best treatment available is not being compared with the new chemical entity. If it is decided to use a nonregistered comparator, it will usually be necessary to submit some chemistry and pharmacy data on the comparator with the clinical trial application. The information required usually includes details of the manufacturer, site of manufacture, and qualitative and quantitative formula details. Obtaining qualitative and quantitative formulation details from an innovator company on their competitor product may be very difficult and may be a reason in itself to opt for a comparator registered in the country.

It is not unusual, therefore, for a European clinical program to use a wide range of comparators depending on the country in which each study is being conducted and the gold standard treatment available. With every comparator, whether or not registered in the country it is usually necessary to manipulate the product to achieve blinding. If significant changes are made to the product, the Annex to the EU Guide (4) states that data should be available (e.g., stability, bioavailability, and comparative dissolution for solid dosage forms) to prove that these changes do not influence the original quality characteristics of the product. The Nordic countries specifically request details of how differences in appearance, taste, and odor between the comparator and the investigational drug are to be masked.

Expiration dating of blinded comparators adds to the complexity of the clinical studies. The expiry date stated on the original package will have been determined for the product in that particular package and may not be applicable to the product repackaged in a different container. The responsibility is on the sponsor to determine a suitable use-by date to be placed on the container. The Annex to the EU Guide states that this date is not later than the expiry date of the original package. Furthermore, if stability data are not generated to support the repackaging, the date should not exceed 25% of the time remaining between the date of repackaging and the expiry date on the original manufacturer's container or a 6-month period from the date of repackaging, whichever is earlier. As a consequence, every additional comparator increases the effort required to provide blinded supplies.

D. Packaging

The Annex to the EU Guide (4) recognizes that packaging and labeling of clinical trial supplies are likely to be more complex and more liable to errors than

with licensed products, because the packaged supplies must often appear blinded. Supply of packaged product for a single study may be subdivided into different packaging batches, perhaps because of the different countries involved in the study, and packaged in several operations over a period of time. As a consequence of the added complexity of the packaging operations, the Annex recommends that supervision procedures, such as label reconciliation, product reconciliation, and line clearance and independent quality control checks, should be intensified.

E. Labeling

There is a substantial diversity in national legislation related to the nature and extent of the information to be included on the clinical trial label and also the language to be used. Such diverse requirements make it difficult to establish core information to satisfy all relevant requirements and thus design standard international labels.

The first edition of the Annex to the EU Guide (4) identified a limited number of core items of information that should be included on every clinical trial label. The revised edition has significantly expanded that list and now states that labels should include the following:

1. Name of the sponsor
2. Pharmaceutical dosage form, route of administration, quantity of units
3. Batch and/or code number (for identification)
4. Trial subject identification number
5. Directions for use
6. For clinical trial use only
7. Name of the investigator
8. Trial reference code
9. Storage conditions
10. Period of use (expiry or retest date)
11. "Keep out of the reach of children" (except if hospital-use only)

Items 1 through 11 should be included on the outer packaging in all cases. Normally items 1 through 7, as a minimum, would appear on immediate packaging unless size precludes. In those cases, items 1, 3 and 5 (plus route of administration for ampoules) would be displayed on the immediate packaging.

Furthermore, each country may have additional specific information that is required in accordance with individual national legislation. These requirements have been the subject of publications by Rosier and Demoen in 1990 (16) and Dupin-Spriet in 1993 (17). The updated labeling requirements following the revision of the EU Annex are provided in Table 1.

	UK (16)	France (16)	Netherlands (16)	Germany (11)	Italy (17)	Spain (17)	Switzerland (18)	Austria (17)	Denmark (16)	Sweden (16)	Norway (16)	Finland (16)
Local language	✔	✔#	✔#	✔	✔	✔			✔	✔	✔	✔ *
'For Clinical Trials'	✔	✔	✔	✔	✔	✔			✔	✔	✔	✔
Study Ref. No.	✔	✔				✔	✔					
Patient name/code	✔											
Drug name/code	✔	✔	✔	✔		✔	✔		✔	✔	✔	✔
Dosage Form				✔		✔			✔		✔	✔
Route of administration		✔		✔		✔			✔	✔	✔	✔
Quantity			✔	✔		✔			✔		✔	✔
Directions for use		✔							✔	✔	✔	✔
Batch No.				✔		✔	✔		✔	✔	✔	
Storage Directions	✔	✔				✔	✔		✔	✔	✔	✔
Cautions/warnings									✔			
Expiry date		✔		✔		✔	✔		✔	✔	✔	
Name of sponsor	✔	✔		✔					✔	✔	✔	✔
Name of manufacturer	✔			✔		✔	✔		✔	✔	✔	✔
Address of manufacturer	✔					✔						
Name of investigator	✔	✔							✔	✔		✔
Keep out of reach of children	✔										✔	

✔ Requirements according to country ruling

Requirements according to EU Annex (4)

Requirements according to Nordic Guidelines (2)

* also Swedish language

\# English acceptable, if a hospital study

F. Expiration Dating and Stability Testing

Generally, a minimum of 3 months' stability data should be provided on the packaged investigational medicinal product to determine the preliminary storage conditions and expiration date (see *Comparators*). The initial expiration date may be quite short and will be continually reviewed as further stability data are collected. The Annex to the EU Guide (4) describes the process for extension of the expiration date of packaged product whereby an additional label including the new use-by date and the batch number may be superimposed over the old use-by date. It is permissible for this procedure to be performed at the clinical trial site by the clinical trial monitor or the clinical trial pharmacist provided the operation is conducted in accordance with standard operating procedures, is checked by a second person, and is fully documented. Samples of each batch of product should be retained in the primary container used for the study or in a suitable bulk container (provided stability data are available to justify the choice of this bulk container) for at least 1 year beyond the final shelf-life, or 2 years after completion of the clinical trial, whichever is longer.

G. Product Release

Unlike marketed products, the Annex to the EU Guide (4) does not require that investigational medicinal products are released by a Qualified Person.

The Annex acknowledges that the production processes involved in the preparation of investigational products may not be validated to the extent that they would be later in development. As a consequence, it is crucial that a highly efficient Quality Assurance system is in operation to control these complex operations.

Shipment of investigational medicinal products to an investigator can proceed only after a two-step release procedure. The first step is release of the product after quality control, described in the Annex as a *technical green light*. The second step relates to the *regulatory green light*. Only when both technical and regulatory approvals are in place can shipment proceed.

H. Product Import/Export

The rules governing the import of clinical supplies into each of the European countries vary. Import licenses or authorization may be required for some countries (e.g., France, The Netherlands and Spain), whereas in Belgium, imported shipments are formally cleared by a nominated Responsible Pharmacist within the country. In Italy, the imported material must also be accompanied by samples of each of the clinical trial supplies, sufficient to permit 10 analytical determinations. However, the revised Annex to the EU Guide (4) now includes a new section on free movement. This states that because investigational products are released (technical green light described previously) by appropriately qualified staff, subsequent analysis after shipping to other Member States is not justified as long as documented evidence is available that appropriate control analysis and release have taken place in the EU. In Norway, the quantity of the imported product must agree with the quantity declared in the Clinical Trial Application.

I. Product Complaints and Recalls

According to the Annex to the EU Guide (4), any complaint should be thoroughly investigated, and the conclusions of any investigation should be discussed between the manufacturer and the sponsor (if they are different) or between the manufacturer and those responsible for the clinical trial to assess any potential impact on the trial.

Recall procedures are particularly important for clinical trial supplies. They should be established written procedures, capable of being initiated promptly at any time and under the responsibility of a nominated individual. They should

be understood by the sponsor, investigator, and monitor, in addition to the nominated individual responsible for recalls.

III. CLINICAL TRIALS IN AUSTRALIA

A. General Comments

The Australian clinical trial application and approval process has undergone extensive revisions since the early 1970s. The current system comprises two options, one based on the CTX scheme in the UK and the other on a clinical trial notification scheme (CTN). The legislative basis for the regulation of clinical trials in Australia is set out in the Therapeutic Goods Act 1989 and Regulations. CTX applications for clinical trials are currently reviewed by the Drug Safety and Evaluation Branch, Therapeutic Goods Administration (TGA), Department of Health and Family Services. Notifications are made to the same organization. Details of requirements may be obtained from the TGA.*

All proposed clinical trials of drugs to be conducted in Australia must be reviewed and approved by an Institutional Ethics Committee (IEC) operating in accordance with the National Health and Medical Research Council (NH&MRC) Statement on Human Experimentation and Supplementary Notes (19). This document, which forms the basis for ethical review of clinical research in Australia, is based largely on the Declaration of Helsinki and subsequent amendments (20). The specific roles of clinical investigators, sponsors, and IECs are outlined in the TGA Guidelines for Good Clinical Research Practice in Australia (21), which were based on the UK, EU, and Nordic Codes of Good Clinical Trial Practice in place at the time. Unlike with the U.S. system, inspection of clinical facilities and investigators is not conducted by the regulatory authorities. The individual IEC is responsible for ensuring that the investigator and facilities are suitable for the proposed study.

B. Regulatory Requirements

Approval of a CTX application or notification through the CTN scheme is required for (a) investigational use of any drug product, including any new formulation that is not included in the Australian Register of Therapeutic Goods (ARTG) and (b) for use in a clinical trial of a currently registered drug product beyond the conditions of its registration approval. Regulatory approval or

*The Information Officer, Therapeutic Goods Administration, P.O. Box 100, Woden ACT 2606, Australia.

notification is not required for use in a clinical trial of a drug product already included in the ARTG if its use in the trial is consistent with the approved product information. In strict legal terms, Australian legislation does not preclude an individual medical practitioner who is not an "incorporated body" from conducting a clinical trial on a registered product for indications or patient populations for which it is not approved. However, in practice, hospitals would be most unlikely to permit any clinical trial without at least IEC approval.

There is no formal link between registration applications and clinical trials in Australia. This means that:

- Applications for registration may be submitted while clinical trials for the same drug are under review or underway.
- Application for notification of a clinical trial may be submitted while a registration application for the same drug is under review.
- There is no requirement for clinical trials to be conducted in Australia before registration approval can be granted for new or modified drug products. The sole criterion for acceptability of a registration package is its scientific and ethical validity.

1. *The CTX Scheme*

The term *Clinical Trial Exemption* refers to an exemption from the general requirement that drugs that are supplied must be registered with the ARTG. The current requirements for application under the CTX scheme have been in effect since July 1992 and are detailed in the document Australian Guidelines: Clinical Trials Exemption (CTX) Scheme for Drugs (22). The UK CTX guidelines (9) were the basis for this scheme. The information required by the TGA includes:

- Particulars of the product and trial.
- Very brief information of the proposed use of the drug in the form of Usage Guidelines.
- Copies of the information to be provided to IECs.
- Overseas status.
- Summaries of scientific data on (a) chemical, pharmaceutical, and biological; (b) pharmaco-toxicological; and (c) clinical documentation in the form submitted in the United Kingdom.
- Documentation of immediately reportable adverse events as required in the United States.

The Usage Guidelines define the indications, dosage forms, dosage, duration of use, and any special conditions that may apply. Further clinical trials do not need separate approval from the TGA if they are within the scope of the Usage Guidelines and have been approved by an IEC.

The TGA takes a flexible approach to scientific data requirements. Although guidelines are provided, reasoned scientific argument that a certain requirement is not appropriate in a particular case will be considered. Data summaries submitted to support a CTX application in the United Kingdom are acceptable and should be accompanied by responses provided to any questions that were asked by the U.K. regulatory agency. A review of the format of the CTX application and requirements in Australia will be undertaken once the proposed EU format for clinical trial applications has been finalized. Under the CTX scheme, the TGA is primarily concerned with ensuring that the proposed trial does not allow an unacceptable safety risk, whereas the IEC is responsible for approval of the trial protocol, including adequacy of the trial design, review of data summaries provided by the sponsor/investigator, and for ensuring that ethical standards are maintained. In contrast to the U.S. system, the TGA does not formally review each trial protocol but instead approves Usage Guidelines as described previously. Because the TGA is supplied only with summary information on available quality, toxicology, and clinical data, scrutiny of CTX applications amounts to negative vetting. That is, the proposal is assessed only for serious safety concerns that would lead to an objection. The system expedites agency review but explicitly places responsibility on IECs for positive vetting.

The timeframe for evaluation by the TGA is 30 working days when applications are supported only by chemistry and quality control data, or 50 working days when applications are also supported by preclinical and clinical data. If the application is acceptable, the sponsor is notified by the TGA that there are no objections to the trial proceeding subject to IEC approval. Applications may be submitted simultaneously to the TGA and to an IEC. The sponsor must relay all the TGA comments, revisions, or objections to the IEC; in a similar manner, the TGA must be notified of any revisions/objections raised by the IEC during its review. If a trial is discontinued for any reason, the TGA should be notified and provided with reasons for the discontinuation.

2. The CTN Scheme

The CTN scheme was introduced in Australia in May 1991 as an optional alternative to the CTX scheme. The CTN option was intended to accelerate the clinical trial review process and to facilitate Australian participation in international clinical trials. Under this scheme, the sponsor needs only to notify the TGA that the trial is to be conducted and provide the signature of an IEC representative to the effect that the study has been considered by the IEC and necessary advice provided. It is specified that the role of the IEC includes review of the protocol, related informed consent forms, and supporting summary data. The TGA does not scrutinize available data but simply records the trial on a database. The regulations permit the TGA to terminate a clinical trial

at any time in the public interest, for example, in the event of a serious adverse reaction. The database permits the TGA to identify all trialists and, in the event of a safety hazard, advise them to take appropriate action. Specific requirements for the CTN scheme are provided in the document Clinical Trials of Drugs in Australia (23).

At present, no regulatory basis governs choice between the CTX or CTN options, and the decision is largely at the discretion of the investigator or sponsor. However, an IEC may require the sponsor to submit a CTX application rather than a notification if it believes that it does not have sufficient expertise to assess all relevant aspects of the proposed trial, particularly with regard to safety. Proposals to conduct phase III, phase IV and bioavailability studies are frequently handled through the CTN scheme, whereas earlier phase studies, particularly for new drugs for which minimal regulatory review has been conducted, may be more appropriately considered through the CTX scheme. However, the CTN scheme is still an option for early phase trials.

The IEC should be provided with all of the information required to adequately assess scientific validity, safety, and ethical implications of a proposed trial. Information that would normally be submitted to an IEC would include a summary statement, the status of the drug in countries with similar regulatory procedures to those in place in Australia (e.g., United Kingdom, United States, Sweden, Canada, and New Zealand), Usage Guidelines, and summary data on chemical, pharmaceutical and biological, pharmacotoxicological, and clinical documentation.

C. Bulk Manufacturing

Under the CTX scheme, the sponsor of a clinical trial in Australia must provide an assurance that investigational products and placebos have been manufactured according to general principles of GMP and in accordance with a therapeutic goods manufacturing license where such a license is required in the country of manufacture. Inspections of manufacturing sites for clinical trial materials are not conducted by the TGA. All manufacturing and packaging batch records should be sufficiently detailed to allow operations to be traced. Records should be retained for at least 2 years after completion of the clinical trial. Guidance on manufacturing and quality control of clinical trial products is provided in the Australian Code of Good Manufacturing Practice (24), Appendix G of which is the EU Guide for manufacture of investigational medicinal products, which has been adopted by the TGA. Sterile products, including placebos and comparator products manufactured by the trial sponsor, should be manufactured to the same standards applied to registered products with respect to process validation and sterility testing. Records of sterilization should be retained, and testing should be conducted according to recognized standards as

described in the Australian Code of Good Manufacturing Practice (25), or current editions of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), or the United States Pharmacopeia (USP). If a product is required to contain an antimicrobial agent, preservative efficacy studies should be carried out to at least the standard of the current USP.

Coloring agents for use in pharmaceuticals for ingestion listed in the NH&MRC Supplement to the Food Standard Code (26) are generally considered to be acceptable; however, this list is soon to be superseded by a document to be issued jointly by the TGA and the National Food Authority.

1. Comparators

The extent of pharmaceutical data required for comparator products is an area of frequent confusion, as sponsors usually do not have access to details such as the method of synthesis of the active ingredient, specifications for each constituent, method of manufacture, etc. The U.K. CTX guidelines, on which the TGA's guidelines were based, specify that pharmaceutical data for comparator products should be provided in a form similar to that required for investigational products, or an explanation should be given as to why the information has not been provided. This is often impractical and the TGA has consequently issued separate notes on the subject of comparator products.

a. Comparator Product Is Registered and Sourced in Australia

A summary of the quality control testing performed on the product by the clinical trial sponsor is generally appropriate. The tests should ensure that batches of the product used in the trial are of adequate quality and would normally include assay, uniformity of content or weight (depending on dose and dosage form), and dissolution rate for solid dosage forms, other than controlled release products for which the appropriate dissolution profile and dissolution test procedure would not be known to the trial sponsor.

b. Comparator Product Is Sourced Overseas, but the Drug Is Registered in Australia for Administration by the Same Route as Proposed in the Trial

If the comparator product is sourced and registered in either Canada, Denmark, The Netherlands, Norway, Sweden, the United Kingdom or the United States, a description of the quality control procedures outlined in the previous section is generally appropriate. More extensive testing may be necessary if the product is sourced from a country other than those listed.

c. Comparator Product Is Sourced Overseas from a Country in Which it Is Registered, but the Drug Is not Registered in Australia, or Is Registered for Administration by a Different Route from that Proposed in the Trial

If the product is sourced from one of the countries listed in the previous section, pharmaceutical data as described in *a.* is usually sufficient. If available, the registration status in each of these countries should be provided. Depending on the circumstances, some safety and efficacy data may be required, which could be in the form of referenced publications.

d. Comparator Product Is not Registered in Australia or in Any of the Countries Specified in b

Full information in accordance with the CTX guidelines is generally necessary.

D. Packaging

Details of the packaging of clinical trial products are subject to review by the TGA under the CTX scheme. A description of the immediate packaging of the products should be provided. If the product is a parenteral, oral, or ophthalmic liquid packaged in plastic or plastic-lined containers, the leaching of additives should normally be tested to a standard at least equivalent to the current USP biological test for plastics. The possibility of leaching of valve components by propellants in metered dose aerosols should be considered.

E. Labeling

The sponsor is responsible for the labeling of supplies, and the protocol should describe how the products are to be labeled. The investigator should check to ensure that the labeling instructions are correct and understood by all subjects. In blinded studies, it must be possible to identify the actual treatment and batch received by an individual subject. The procedure for breaking the treatment code should be clearly specified in the protocol. If an application is lodged through the CTX scheme, labels are subject to review by the TGA. The following summary of noncompulsory guidelines for labeling is offered by the TGA if advice is requested:

- *Placebo Controlled or Blinded Trials*: Labels should include the patient identification number, trial identification, expiration date (of the least stable blinded product), storage conditions, and special instructions (e.g., "swallow tablet whole").
- *Nonplacebo Controlled and Open Trials*: Labels should include names of all drugs present and their quantity or proportion, batch number, expiration date, trial identification, storage conditions, and special instructions.
- *Radiopharmaceuticals*: In addition to the details given above, labels should also include a statement that the preparation is radioactive, the total radioactivity in the container at a stated hour and date, and the volume of liquid in the container.

The recommended storage temperature should be specified on the label. Acceptable storage temperatures include (a) below −18°C (deep freeze), (b) below −5°C (freeze), (c) below 8°C (refrigerate), (d) between 2°C and 8°C (refrigerate, do not freeze), (e) below 25°C, and (f) below 30°C. These temperatures reflect actual conditions that are likely to be encountered in freezers, refrigerators, and air conditioned and non-air conditioned premises, respectively. In cases where no shelf-life has been set for the product, an expiration date may be omitted from the label if all of the conditions described under Expiration Dating and Stability Testing are met.

Where the container has a volume of less than or equal to 10 ml and is enclosed in a primary pack containing the details described previously, the expiration date, storage conditions, and special conditions may be omitted from the label on the small container.

F. Expiration Dating and Stability Testing

For applications lodged through the CTX scheme, it is generally recommended that the results from a minimum of 3 months' stability testing at a maximum recommended storage temperature be available in cases where stability data are insufficient to allow determination of a shelf life and storage conditions. In addition, in such cases, a certificate of analysis (less than 3 months old) on the batch to be used in the trial containing results of all quality control tests and bearing the date of testing should be held by the Australian sponsor from the time of the commencement of the trial. Further certificates should be generated at at least three monthly intervals from the first testing date until completion of the trial, and these data should be scrutinized by the Australian sponsor. If the on-going stability testing suggests a problem, the batch should be withdrawn, and new batches may then be substituted.

G. Product Release

Standards applied to clinical trial investigational products or placebos are generally the same as those required for registration, with certain exceptions for packaging and labeling. Standards described in the BP or Ph.Eur. are generally acceptable in Australia. In addition, USP standards are acceptable for active raw materials and finished products in clinical trials, and for active raw materials at registration. In certain instances, new standards have been issued in Australia by way of a Therapeutic Goods Order (TGO). Normally, TGOs take precedence over other standards, but BP, Ph.Eur., and USP standards are normally acceptable for clinical trial materials.

Suitable quality control testing is critical because the manufacturing processes may not be fully validated or standardized at the time of manufacture of clinical trial supplies. Each new version of specifications (for starting ma-

terials, primary packaging materials, intermediate and bulk products, and finished products), manufacturing formula, and processing and packaging instructions should be documented and the rationale for changes should be recorded. Excipients in investigational products or placebos should comply with appropriate specifications. Samples from each batch of product to be used in the trial should be retained (in the primary container or a suitable bulk container) for 1 year longer than the shelf life of the product for future quality assessment.

The TGA believes it is important to test placebos for the absence of active drug, as there are recorded instances in which placebo and active batches were inadvertently interchanged or mixed, and one instance in which a batch of placebo contained a trace of active drug.

H. Product Import/Export

Under the Therapeutic Goods Act 1989, special approval must be obtained from the Secretary of the Department of Health and Family Services for the importation, exportation, or supply of therapeutic goods to be used solely for experimental purposes in humans, unless the goods are included in the ARTG. The importation of certain groups of substances, including antibiotics (both raw materials and finished products for human or veterinary use), anabolic steroids, growth hormones, narcotics, psychotropic drugs, and certain specifically prohibited substances, is subject to additional restrictions. Materials of biological origin, whether human, animal, plant, or bacterial, require quarantine clearance before importation into Australia.

Materials supplies under the CTN scheme are exempt from the requirement for importation approval under the Therapeutic Goods Act 1989, although the requirements of other legislation may apply, including those related to drugs of dependence, customs (prohibited substances), and quarantine.

I. Intermediate Storage and Dispensing to Investigators

The sponsor should make arrangements to supply the clinical trial products to the investigator; and details of shipment, receipt, dispensing or distribution, return, and disposal of drug supplies should be accurately documented. The TGA strongly recommends that a pharmacist or pharmacy department be responsible for accepting delivery, storage, and record keeping for all drug supplies. It is the investigator's responsibility to ensure that the drug supplies are securely and appropriately stored and handled. All unused supplies, including investigational products, reference products, and placebos, should be returned or destroyed as agreed with the sponsor and accurate records of complete drug accountability should be kept according to the protocol. Leakage of trial materials to nontrial use without sponsor and IEC authorization is illegal. On the other hand, the TGA allows continued use of the drug after the trial has fin-

ished if it has proved beneficial to particular patients and provided both the sponsor and the IEC approve. Indeed, this practice is encouraged if there is no alternative therapy.

Both the sponsor and the investigator should retain records and data for at least 15 years after the completion of the study and preferably for the lifetime of the product. All documentation related to the study, including any correspondence between the sponsor and the investigator, or correspondence with the regulatory authorities, should be retained. If the investigator becomes unable to maintain the documentation, the sponsor should be notified in writing of the location of the records and the person responsible for the records. If necessary, the sponsor may retain the investigator's documents.

IV. CLINICAL TRIALS IN JAPAN

A. General Comments

Data obtained from clinical trials in Japanese healthy volunteers and patients are an essential requirement in any regulatory submission for a Japanese NDA application. It is obligatory to submit data on human pharmacokinetics (in Japanese subjects) and to conduct a formal dose-finding trial and a comparative efficacy trial (both in Japanese patients). Human pharmacokinetic studies are usually performed in Japanese healthy volunteers, except in the case of cytotoxic agents and potent hormonal agents. In general, all such trials must be conducted in full compliance with the Declaration of Helsinki (20) and with Japanese guidelines for Good Clinical Practice (27). Since September 1996, the Japanese GCP guidelines have been undergoing revision in line with ICH recommendations. The finalized new guidelines were published in April 1997 and are expected to be implemented during 1997.

It is also important for a foreign sponsor of Japanese trials to appreciate the normal custom and practice relating to clinical trials in Japan. This section on Japanese trials is therefore written from the perspective of a non-Japanese international company with plans to conduct clinical trials in Japan. The aim is to provide insight into some of the less familiar procedures of Japanese trials and to explain those aspects for the benefit of the Western reader.

Until 1983, it was impossible for a non-Japanese company to make a direct application for manufacturing approval in Japan. NDA applications from foreign companies, therefore, were possible only after formal co-development arrangements had been established with Japanese manufacturers. In 1983, with the amendment of the Pharmaceutical Affairs Law, direct applications were permitted, and it became possible for a non-Japanese applicant to initiate clinical trials in Japan. Even under the amended legislation, it is essential for a non-Japanese sponsor to provide (or have access to) locally based support staff who

can manage the planned trials. Such support may now be provided either through a formal collaboration with a Japanese company, or through the appointment of a clinical trial caretaker who agrees to provide local staff to manage the planned trials. A useful overview of the general requirements for clinical trials in Japan (including some clinical guidelines) is available in Drug Registration Requirements in Japan (5th Edition) (28). There is also a chapter on Handling of Clinical Trials in the comprehensive English-language text Drug Approval and Licensing Procedures in Japan 1995 (29). The obligations of the clinical trial sponsor are also set out in Articles 67, 68, and 69 of the Enforcement Regulations of the Pharmaceutical Affairs Law. For information on these regulations, see Standards and Certification Systems concerning Drugs in Japan (30), as well as Drug Approval and Licensing Procedures in Japan (29).

The singlemost important factor to appreciate about the administration of clinical trials in Japan is that a greater deal of influence is automatically vested in the senior investigators who are conducting the trials. Most pharmaceutical companies in Japan (whether foreign-owned or Japanese companies) do not have staff clinicians, or even a Medical Director. Instead, the clinical aspects of trials are conducted entirely by external investigators who work on a consultancy basis. Phase I studies (in healthy volunteers) are performed in some hospitals or within specialized contract research organizations, and they are conducted under the clinical responsibility of an appropriate investigator (e.g., the clinic's chief investigator). Patient studies in phases II and III are often conducted on a multicenter basis, by a specially recruited group of hospital clinicians, who are led by a Principal Investigator (also known as Key Investigator). The Key Investigator is often an opinion leader in the relevant clinical specialty or disease class and therefore has great power and influence and will often introduce other investigators from among his regular collaborators. (As part of the ongoing revision of the GCP guidelines, the role of the Key Investigator is expected to be abolished. After April 1997, phase II and III trials are expected to be run by Coordinating Committees).

For ethical reasons, Japanese investigators are reluctant to accept placebo-controlled designs for efficacy studies (they consider it unreasonable for some patients recruited into clinical trials to receive no effective treatment). Against this background, the regulations require that the pivotal phase III efficacy trial in a Japan development program is often conducted as a double-blind comparator-controlled study. However, in practice, recruitment may be limited to about 240 to 400 patients (i.e., 120 to 200 patients per arm). The phase III efficacy data will often be augmented by results from several open trials conducted in parallel with the double-blind trial. Even so, it is not unusual for a full NDA clinical development program (in a single indication) to be based on a total patient population of 700 to 800 patients (plus 50 to 80 healthy male volunteers in the phase I studies).

Although the clinical expertise is provided by the consultant investigators' group, it is the sponsor's responsibility to supply the necessary administrative support and monitoring resources to control the trials (as laid down in Articles 67, 68, and 69 of the Enforcement Regulations of the Pharmaceutical Affairs Law and in the Guidelines for Good Clinical Practice). The finalization of study designs, preparation of protocols, review of case report forms, and compilation of data into external publications is overseen by a coordinating committee of the senior investigators, in collaboration with representatives from the sponsor. Through this committee, the sponsor has an opportunity to exert influence on the design of the trials and the interpretation of the results. However, although many Japanese investigators will be happy to adopt Western study designs, others may prefer traditional study designs, which are more in line with Japanese custom and practice.

The language for all official documents (protocols, case report forms, Investigator Brochures, clinical trial contracts, etc) is Japanese. Since neither English nor any other European language is acceptable as an alternative, the sponsor must have access to appropriate Japanese support staff.

B. Regulatory Requirements

At present, there is no formal system of prior regulatory approval before clinical trials can be initiated in Japan. Apart from mandating the review of draft protocols by appropriate Ethics Committees (Institutional Review Boards), the Ministry of Health and Welfare (MHW) currently permits clinical trials to be conducted on the clinical responsibility of the investigators. Even so, notification of each clinical trial to the MHW is required, and this is accomplished via a CTN scheme. In support of the CTN, the protocol, case report form, text for obtaining Informed Consent, ethical and scientific rationale for the study, and an Investigator Brochure are submitted to the MHW. In principle, the MHW has the power to disallow any submitted CTN, but objections are rarely lodged in practice. The CTN process is also used to facilitate (and control) the importation of clinical trial supplies from outside Japan. Beginning in April 1997, as part of the revision of the GCP guidelines, the MHW implemented a prior approval system, which appears to be similar to the IND procedure used in the United States. Under the proposed new procedure, sponsors of clinical trials will not be permitted to initiate any phase I trial until 30 days have elapsed after submission of the necessary documentation. The MHW may return comments to the sponsor within the 30-day review period.

The Investigator Brochure, which supports the CTN, (or the new IND), should provide a comprehensive summary of the preclinical data (i.e., tabular summaries of the toxicology, pharmacology, and metabolism) together with information on the proposed clinical indication. The chemistry/pharmacy data

included in the brochure need not be as extensive as in many U.S. or European brochures. Results from any previously completed trails in Japanese subjects or patients are often included, together with brief summaries of pivotal trials conducted outside Japan (included for the first CTN only). Indeed, the Investigator Brochure is usually revised at the start of each new clinical phase, so that data from the latest Japanese trials can be added.

In addition to the checks and controls provided by the CTN process, a further level of review is delegated to Institutional Review Boards (IRBs). Study protocols must be reviewed ethically and scientifically by an IRB in each hospital. After acceptance of the protocol by the IRB, a formal legal contract between the hospital and the sponsor is required before a trial can be initiated at a given center.

C. Bulk Manufacturing

1. GMP

Although approved drugs must be manufactured in compliance with the Good Manufacturing Practice Regulations of Japan (4th Edition) (31), there is no specific requirement for clinical trial supplies to be manufactured under GMP. The MHW, therefore, do not conduct inspections of manufacturing facilities for clinical trials materials, either in Japan or elsewhere. Even so, the MHW recommend that the manufacturing of clinical trial materials should be conducted in full compliance with GMP. Moreover, when conducting GCP inspections, the inspectors usually expect to audit available records to the quality of the trial supplies (such as Certificates of Analysis supplied by the manufacturer, and records of importation and packaging). For a sponsor with limited manufacturing facilities in Japan, there is no major difficulty in arranging for clinical trial supplies to be shipped into Japan from Europe or the United States (see Product Import/Export). In March 1997, the MHW issued new guidelines on the manufacturing of clinical trial supplies and on the facilities where such manufacture can be conducted (so-called cGMP guidelines). The full impact of these guidelines (34) will become available during 1997.

2. Approved Excipients

The excipients used in approved drugs in Japan are normally those listed in the current Japan Pharmacopoeia (JP), in Japan Specifications for Pharmaceutical Ingredients (32), or in Japan Pharmaceutical Excipients (33). In general, therefore, although there are no specific regulations in relation to clinical trial materials, it is helpful if clinical trial formulations also utilize only the ingredients listed in those references. When a sponsor is committed to a formulation that includes a nonapproved excipient, such a formula may be used for trials, provided the senior investigators can be reassured as to the excipient's safety and

importance to the formulation. There is no Drug Master File system in Japan; therefore, once the NDA dossier is submitted to the MHW for regulatory review, the applicant will then need to seek approval for the new excipient by submitting the necessary data to the Additives Subcommittee of the MHW. By this means, the approval of an unlisted additive can usually be sought in parallel with the regulatory review of the main NDA file.

As a consequence of BSE (bovine spongiform encephalopathy) being seen in some herds of British cattle in recent years, the MHW have ruled that excipients normally isolated from beef tallow (such as magnesium stearate and polysorbate 80) and from other ruminant sources can be used in Japan only if they can be shown to originate from non-U.K. sources.

3. Size and Shape of Dosage Forms

For ethical drugs, there are no formal regulations on the size and shape of dosage forms in Japan. Indeed, there is a wide variety of tablet shapes and colors among existing products. Despite these factors, there is a current tendency for new tablet formulations to be round, white, plain, bi-convex, and relatively small (e.g., typical diameter of 8 mm or less), in line with the perceived preferences of patients. Similarly, gelatin capsules are typically not larger than Size 3 (15.9 × 5.8 mm diameter). Such constraints will sometimes limit the maximum strength of the dosage form, and in those situations, it is preferable for the presentation to be two or more units of lower strength, rather than a single larger dosage unit.

Approved coloring agents are used (albeit rarely) to distinguish tablet strength, for example. Even so, pale colors are often considered more acceptable than strong colors.

4. Comparators

Although the sourcing of comparator products can be a major difficulty in some countries, it is a feature that has been particularly well organized in Japan. An agreement concluded by members of the Japan Pharmaceutical Manufacturers Association (JPMA) provides for the supply of unmarked comparators (and matching placebo) to the trial sponsor, by the approved Japanese manufacturer of the chosen comparator product. Although not formalized in government legislation, the procedure adopted by the JPMA virtually guarantees the availability of appropriate gold standard therapy for use in phase III comparator trials. The process is initiated by the selection of the most appropriate comparator at a meeting of the senior investigators. The manufacturer of the selected comparator is then approached with a request for supplies, supported by the sponsor's protocol. After review and acceptance of the protocol (which is often based on a double-dummy design), the comparator supplies are promptly

provided (at cost) to the sponsor. Packaging and distribution of all the supplies are then completed by the sponsor in the usual way.

D. Packaging

There are no formal regulations governing the packaging of clinical trial materials in Japan. In practice, blister packaging is frequently used as the primary packaging for tablets or capsules; ampoules or vials are packed in simple trays. The primary pack is then contained in a simple carton, which must be labeled (in Japanese) in line with government legislation (see Labeling).

When the supplies are sourced from a manufacturing facility outside Japan, it is invariably less complicated for packaging and labeling to be completed in Japan, rather than in the country of manufacture. This is particularly recommended for controlled trials, where the comparator is most likely to be sourced within Japan.

E. Labeling

1. Minimal Requirements

Information that must (and that must not) be supplied as part of the labeling for clinical trial materials is laid down within the Enforcement Regulations of the Pharmaceutical Affairs Law (Article 67). Thus, the following shall be printed in Japanese on the "containers or wrappers, or on the drugs" (interpreted to mean the primary or secondary packaging, or the dosage forms):

- A statement that the material contains an investigational drug
- Name and address of the sponsor (or if not resident in Japan, the sponsor's name and country and the name and address of the Japanese "caretaker")
- Chemical name or identification code of the drug
- Lot number or production code
- Recommended storage conditions and shelf life (or expiry date), if necessary

By contrast, the following information *must not* be given in the documents attached to the investigational drug, on the drugs themselves, or on their packaging:

- Proposed trade name
- Proposed indication, effects or performance
- Proposed administration and dosage

2. Approval of Labeling

Provided that the labeling meets the minimum requirements of the Pharmaceutical Affairs Law, there is no need for governmental approval of the labeling

for clinical trial supplies. The sponsor, therefore, may decide what labeling is appropriate.

3. Blinding and Randomization of Clinical Trial Supplies

Although some Japanese trials are conducted using an open design, the pivotal phase III patient study will often follow a double-blind, double-dummy, comparator-controlled study design (or may, rarely, be placebo-controlled where no existing therapy is yet available). In these situations, the quality and packaging of blinded supplies are primarily the responsibility of the study sponsor. However, it is also usual for the overall quality of the investigational supplies to be monitored by an impartial third party (e.g., staff at a nominated university). Although there are no formal regulations for the subsequent randomization of blinded supplies, it is usual to delegate the responsibility to a selected investigator, who is known as the Study Controller. The Controller is singularly responsible for overseeing the randomization of blinded supplies, for safeguarding of the randomization code during the study, and for breaking the code, if required in an emergency. If there is any doubt as to the adequacy of blinding, the Study Controller's decision is final.

F. Expiration Dating and Stability Testing

In Japan, there are no formal regulations or guidelines concerning the setting of shelf life and/or expiry dates for investigational new drugs. Nevertheless, guidance from the MHW recommends that appropriate stability studies should be conducted by the sponsor, to ensure the quality of the trial supplies throughout the study period. The results of such stability testing are not usually submitted to the MHW as part of the regulatory dossier for NDA approval, but the data may be called for review as part of the GCP inspection, which is conducted after NDA submission.

G. Product Release

Few regulations govern the release and distribution of clinical trial materials in Japan. Nevertheless, it is usual for clinical trial materials (whether imported or supplied from a local source) to be routinely subjected to QC testing on arrival at the sponsor's facilities. Having confirmed that the materials are of suitable quality, the sponsor (or the clinical trial caretaker) has responsibility for distribution of the supplies to the institutes who are to participate in the trial. Under the Enforcement Regulations of the Pharmaceutical Affairs Law, the sponsor (or caretaker) must not delegate distribution to a third party. Also, the clinical trial supplies may not be distributed to a given institute until after the signing of a formal contract between the institute and the sponsor. Finally, the Enforcement Regulations specifically require the sponsor to retain records of the manu-

facture, importation, and QC testing of the materials, and of the dates of distribution and quantities distributed to individual hospitals. In addition, although it is not a formal regulatory requirement, the MHW recommend that the sponsor should store retained samples of all clinical trial materials until after the GCP inspection and/or completion of the first committee-stage of the NDA regulatory review (so-called first Chosakai review). Information related to product release is also included in the new cGMP guidelines, issued in March 1997 (34).

H. Product Import/Export

The importation of clinical trial materials into Japan (from Europe or the United States) does not usually require any import license or specific authorization beyond that which is automatically granted through the CTN procedure. For trouble-free importation of supplies, it is advantageous to meet the following requirements:

- The supplies should be shipped by air-cargo and formally imported through Japanese Customs, rather than by use of any courier service.
- The quantities imported should be reasonably in line with the study requirements, as outlined in the CTN.
- Certificates of Analysis should be provided with the materials to show that they meet the current specification of the manufacturer and to show the expiry date of the materials.

I. Product Complaints and Recalls

There are no formal regulations in Japan governing the recall of clinical trial materials in the event of a complaint in relation to quality. However, some guidance is given in the new cGMP guidelines, issued in March 1997 (34).

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15

Blinding Clinical Trial Supplies

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I. INTRODUCTION: RATIONALE FOR BLINDING CLINICAL TRIAL DRUGS

The manufacture, packaging, and labeling of drugs for clinical trials differ in several important ways from preparation of marketed drugs. A common concept of marketing in any field is *product differentiation*. The seller tries to make the product unique in some way, so that customers will remember and purchase the product. For marketed pharmaceutical products, this may involve use of unique shapes, colors, markings, packaging, and labeling. This concept of product differentiation for market products is in sharp contrast to the requirements for drugs manufactured, packaged, and labeled for use in blinded clinical studies.

One of the most significant differences between marketed pharmaceutical products and clinical trial materials is that many clinical studies require *blinding* of the drugs. One dictionary definition of blinding is to hide or conceal. In a blinded clinical study, the objective is to hide or conceal the identity of the drug treatment. Blinded clinical studies are usually intended to compare the safety and efficacy of investigational drug therapy with the known effects of marketed drug therapy or no drug therapy (placebo control). Clinical studies are blinded to prevent bias by the participants in the evaluation and reporting of study results. Blinding may involve concealing the drug treatment from one or more of the clinical study participants. Table 1 defines common types of blinding used in clinical studies.

To effectively blind a clinical study, all aspects of each treatment must appear to be the same. The dosage forms, packaging, labeling, the dosage intervals, and the quantity of dosage form administered should all be identical to prevent disclosure of the drug treatment and the bias that may result. The dosage forms to be blinded may include several potencies of the study drug, placebo, and one or more formulations and potencies of comparator or positive control drug (e.g., a marketed, commonly used drug for the indication

TABLE 1 Common Types of Blinding Used in Clinical Studies

Open Label:	No blinding is used; participants know the identity of the treatment.
Single Blind:	Only the patient is blinded.
Double Blind:	The patient and clinical investigator are blinded.
Triple Blind:	The patient, the clinical investigator, and the sponsor are blinded.
Double Dummy:	Using active and placebo dosage form of *both* the study drug and the positive control drug or drugs to blind a study.
Third Party Blinding:	Use of an unblinded third party (e.g., pharmacist or nurse) to dispense drugs to blind a study.

being studied). The techniques used to do the blinding, while still complying with all aspects of good manufacturing practices (GMP) requirements, are key reasons why manufacturing, packaging, and labeling of clinical materials are a distinct specialty within the pharmaceutical field. In addition to being good science, there are two other primary reasons for conducting blinded clinical studies.

A. Economic

Blinded studies can enhance marketability of a product by demonstrating favorable health economic advantages. Greater therapeutic efficacy, fewer adverse effects, or other advantages for the investigational drug when compared in a blinded clinical study with marketed drugs or placebo a can result in preferential use of the new drug by private physicians, and placement on the formularies of hospitals and health maintenance organizations, or government purchasers. The advantages may also aid in justifying a higher price for a newer, safer, more effective drug.

B. Legal

Many governments require blinded clinical studies for approval of a new drug in the United States, 21 CFR 314.26 discusses "Adequate and well-controlled studies." Paragraph (b) (2) of that regulation states, "The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect." Paragraph (b) (5) states, "Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data." In the European Economic Community (EEC), or European Union (EU), Directive 91/507/EEC states, "In general, clinical trials should be done as 'Controlled Clinical Trials', and if possible randomized; any other design shall be justified. The control treatment of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than the effect of a placebo." These requirements can be effectively met by conducting double blind clinical studies.

C. Blinding Considerations

As previously stated, all aspects of the dosage form, packaging, labeling, dosage intervals, and quantity of dosage form administered should be the same to effectively blind a clinical study. Specifically, it is important to consider the drug treatment in terms of the five senses, and every effort should be extended to mask any potential deviations, including those in Table 2.

TABLE 2 Points to Consider when Blinding Treatments

Sight—size, shape, color, markings, packaging, labeling
Smell—odor of the dosage form or vehicle
Sound—a tablet inside a capsule must not rattle
Taste—mask any unique taste of study drug and comparator
Touch—coatings, isotonicity, viscosity, route of administration

This chapter focuses on details of some important considerations in the manufacture, packaging, and labeling of materials for blinded clinical studies within the constraints of GMP requirements.

II. METHODS OF BLINDING POSITIVE CONTROL DRUG DOSAGE FORMULATIONS

Background

In the ideal situation, the positive control drug (PCD) used in a comparative, double blind clinical study would be identical in appearance and dosing to the investigational drug. In real life, this seldom, if ever, occurs. Marketed drugs are available in an almost infinite variety of size, shape, and color. In addition, there are differences in the route, volume, and interval of administration, and unique packaging for many marketed drugs. It is critical to consider stability and bioavailability to ensure that the drug is fully potent and available to have a valid comparison. In addition, it is important to ensure that the PCD and investigational drug are prepared to maximize patient compliance with the dosage regimen. These facts make every new effort to prepare a blinded PCD a challenge. The challenges would be significant even if time constraints were not a consideration. Invariably, however, economic and ethical concerns require resolving the challenges in the shortest possible period of time to support New Drug Applications (NDA). Developing a positive control drug can mimic the process of developing a new investigational drug. The process can be costly and time consuming. Following are some of the key considerations when a PCD is needed for an investigational drug study:

1. *Availability of drug substance for purchase, and analytical methods*: Is this a relatively new, patented, proprietary product, or an established, official compendial product (i.e., U.S.P., B.P., E.P., J.P.)?
2. *Stability of dosage form in proposed clinical trial packaging*: Will stability studies be required to ensure potency of the drug in the packaging used?

3. *The Manufacture and Control section*: Does the IND, CTX, or equivalent document include all required information for the PCD?
4. *Bioequivalence of the PCD with marketed formulations of the compound*: Will the release and absorption of the PCD in the patient compare favorably to the marketed drug?

Three general possibilities exist for preparation of positive control drugs:

1. Obtain the PCD product directly from a firm that markets the formulation.
2. Manufacture and test the PCD "from scratch," either (a) from commercially obtained chemical substance or (b) from chemical substance obtained from an innovator firm.
3. Purchase and reprocess or manipulate the marketed formulation.

There are pros and cons for each of these three methods. The specific method of blinding PCDs for a particular clinical study must be based on a careful review of the drug product itself and any pertinent logistical, timing, business, regulatory, and policy issues involved. The final decision for each PCD should be determined on a case by case basis. Figure 1 is a decision tree to help determine the appropriate method.

The great majority of blinded, comparative clinical studies using PCDs involve solid, oral dosage formulations (e.g., tablets and hard gelatin capsules). Therefore, this section concentrates primarily on blinding of solid, oral drugs, and will comment only briefly on liquid oral, ophthalmic, or topical products, parenteral products, creams, ointments and lotions, aerosols, and transdermal products.

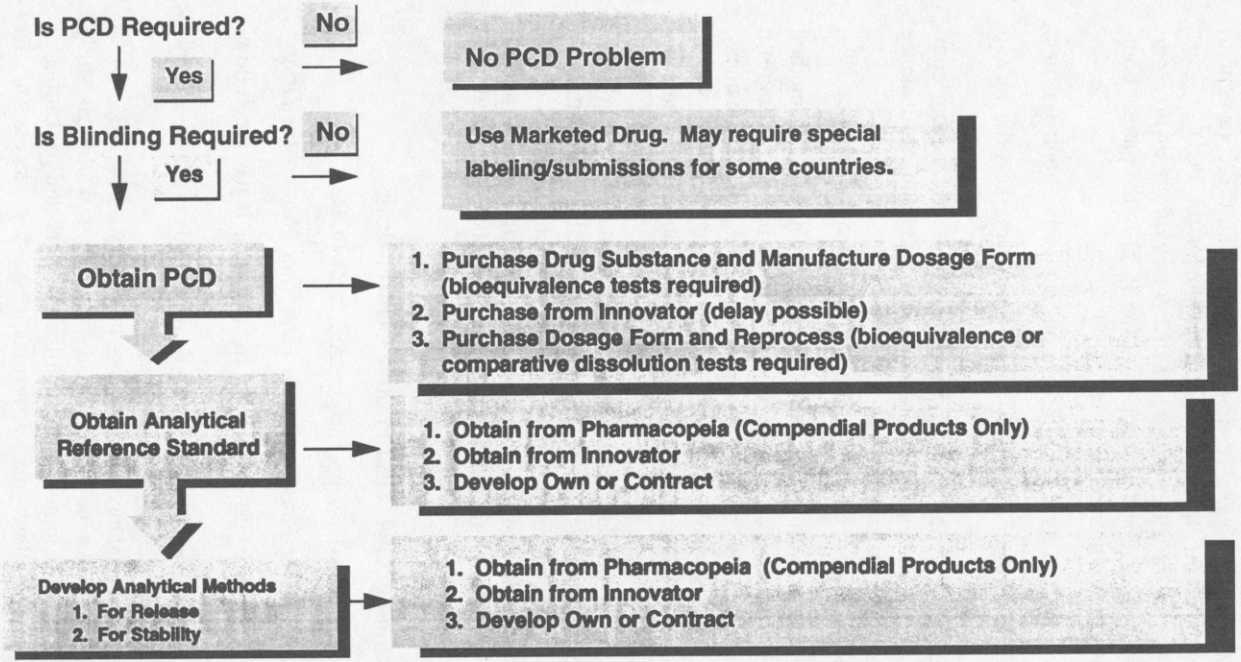
B. Blinding Solid, Oral Positive Control Drugs

Following are common methods of preparing solid, oral PCDs.

1. Obtain PCD and Matching Placebo From a Firm That Markets the Drug

When possible, this offers the best solution in many cases. It has the following potential benefits:

- Developing dosage formulation and analytical methods is not necessary.
- Supplier may provide identity testing method.
- Bioavailability/bioequivalence testing is not necessary.
- Stability testing may not be necessary if the proposed clinical study packaging is equal to or more protective than the marketed packaging.
- The supplier may allow the government agency access to its Manufacturing and Control submission (e.g., IND or CTX) on behalf of the firm doing the clinical study.



Special Considerations:

1. The manufacture and testing of Positive Control Drugs must be described in regulatory submissions (e.g. IND and CTX).
2. Generally, a placebo matching the Positive Control Drug will be required to facilitate a "double dummy" study unless the PCD and study drug are identical.
3. Innovators are often reluctant to provide analytical methods, as these may be considered proprietary information.
4. The manufacturer and formulation of marketed drugs may vary from country to country, complicating global clinical studies.

This option has some potential obstacles or disadvantages.

- Noncooperation by the firm marketing the drug
- Loss of timing control if dependent upon the other firm's schedule
- The supplying firm may require review of the study protocol.

The process of obtaining a PCD from another firm is discussed later.

2. *Clinical Dosage Form Is Manufactured Using Purchased New Drug Substance*

This is most feasible when the PCD is an official compendial product (U.S.P., B.P., J.P., etc.), because the compendia may contain a formula, as well as analytical methods for the product, and the specifications which it must meet. The official formula, tests, and specifications must be strictly followed. The primary benefit of this method is that it does not require the cooperation or involvement of another firm that markets the product. There are many disadvantages to this method, particularly if the product is not an official, compendial drug:

- A suitable formulation must be developed, if it is not compendial.
- Analytical methods must be developed, if it is not compendial.
- Complete in vitro testing must be done.
- Manufacturing and Control data must be submitted to the regulatory agency (e.g., FDA in the United States).
- Stability testing is necessary.
- The need for bioavailability/bioequivalence testing must be evaluated on a case by case basis.

3. *Obtain New Drug Substance (or Granulation, or Powder Fill) from a Firm that Markets the Drug and Compress Into a Tablet or Encapsulate into a Hard Gelatin Capsule According to the Marketing Firm's Instructions*

This option has the following potential benefit: bioavailability/bioequivalency testing and stability testing may not be necessary.
The obstacles or disadvantages are:

- In vitro testing must be done to ensure compliance with the specifications of the marketed product
- Manufacturing and Control data must be submitted to the regulatory agency (e.g. FDA in the United States)
- The disadvantages listed in the preceding paragraph may apply.

4. *Purchase and Reprocess a Marketed Product Through One of Several Methods*

The degree of difficulty required to prepare blinded solid oral PCDs using this option is determined primarily by the size and shape of the marketed formulation, and whether or not the marketed product has enteric coating. There are

many possible options for reprocessing a marketed product. Following are the most common.

- Overencapsulation of the marketed product in an opaque, hard gelatin capsule. If the formulation is a small tablet or capsule, it may be possible to insert the marketed dosage form into an capsule. Addition of an excipient is normally required to prevent the capsule from making a rattling noise when shaken. Automated equipment is available to insert a tablet or capsule into a hard gelatine capsule, overfill with excipient, and checkweigh each capsule to ensure that it was filled correctly. This can also be done by hand. Some contract firms provide this service as well.
- Put a light film coating over a marketed tablet and prepare matching placebo.
- Put a thin coating of excipient over marketed tablet and recompress.
- Breaking or grinding the marketed tablet or capsule and either compressing into a tablet or encapsulating into an opaque hard gelatin capsule to match the investigational drug. This method cannot be used satisfactorily if the marketed product has an enteric coating (i.e., either an enteric tablet or enteric beads in a hard gelatin capsule.
- Removing markings from marketed tablets or hard gelatin capsules by a method that does not affect the product's stability or bioavailability. The marking ink on many marketed tablets or capsules can be removed by using an alcohol swab. It may also be necessary to empty out some of the unmarked capsules and refill them with an excipient, for use as placebo.

These five methods have one common benefit: The cooperation and involvement of a firm that markets the drug are not required, thus the timetable can be controlled directly. There are numerous obstacles or disadvantages, which vary in degree depending on the method used:

- Analytical methods must be obtained and testing done to ensure that in vitro attributes of the reprocessed product compare favorably with those of the original marketed product.
- Stability testing is necessary.
- Bioavailability/Bioequivalence testing must be evaluated on a case by case basis. This will be required for major reprocessing of a marketed product.

C. Positive Control Drugs for Nonoral, Nonsolid Dosage Forms

The myriad potential differences between other types of dosage forms requires careful consideration on a case by case basis. General rules for preparation of blinded dosage forms are of little value for these products. For some of the dosage forms listed below, it may be necessary to use an alternate method of blinding, such as unblinded third parties to prepare and administer the dosages,

or special packaging to mask any differences in dosage form. These alternate, nondosage form types of blinding will be discussed later. If attempting to blind the dosage form itself, following are some aspects that must be considered.

1. Liquids, Creams, or Ointments for Oral, Ophthalmic or Topical PCD Formulations

Preparation of liquid, cream or ointment PCDs is highly dependent on the properties of the comparator drug product. Special consideration must be given to color, odor, opacity, and viscosity for all liquid products. Taste is important for oral liquids, and isotonicity is critical for ophthalmic liquid products. Efforts to match properties of the investigational drug and PCD are made extremely difficult by the need to ensure that coloring, flavoring, or other agents to mask differences must be added without affecting the bioavailability or stability of the products. On aging, some solutions will exhibit a color change, which must be considered when preparing a PCD. Maintaining the sterility of ophthalmic products can also add to the difficulty of preparing these PCDs.

2. Parenteral Positive Control Drug Formulations

Parenteral products will include sterile solutions, which may be viscous or nonviscous, and sterile lyophilized plugs or sterile powders for reconstitution. Each of these offers its own challenges. Because parenteral doses must be liquid or dispersed, many of the considerations mentioned for the liquid, cream, or ointment products are also important for parenteral drugs. Maintaining sterility and stability is important. For parenteral drugs that must be reconstituted or diluted before administration, if the fluids or volumes used to reconstitute or dilute them are different, this can also unblind the study.

3. Aerosols

Some groups who perform many clinical studies with aerosols have gone so far as to develop special equipment to encase the primary aerosol container to blind the packaging differences between the marketed and investigational drugs. Aerosols may be a gas, liquid, or fine powder. In addition, they may be for topical, oral, or inhalation dosing. The attributes of a specific investigational drugs and PCDs will dictate whether effective dosage form blinding may be accomplished, but in most cases it is advisable to use nonformulation related blinding such as unblinded third parties or special packaging, which are discussed later.

D. Special PCD Considerations for Multinational Clinical Studies

Preparation of PCD formulations for multinational studies presents some requirements that demand special consideration. These relate in particular to (a) the formulation of the PCD itself; (b) use of dyes or coloring agents, preser-

vatives, or certain excipients; (c) the regulatory status of the PCD in specific countries; and (d) marketing considerations.

1. Formulation

Whether a drug is marketed by the same firm worldwide, or by different firms in various countries, the formulation is not necessarily the same from country to country. This raises special issues for use of a PCD in global clinical studies. It is important to verify the similarity of a formulation before initiating such a study. A bioequivalence study comparing different formulations may be required. If manufacturing a PCD from scratch, the sponsor of a global study may need to conduct bioequivalence studies comparing the manufactured product to marketed products having different formulae. If obtaining a PCD from a firm that markets it, it may still be necessary to perform bioequivalence studies with marketed formulations, which are different from the PCD used. In the case of controlled release dosage forms, a time-release study may also be required. The need to perform these studies must be considered for any global study using a PCD. This is especially important if the clinical data from multiple countries are pooled for a government regulatory submission.

2. Dyes, Coloring Agents, Preservatives and Excipients

The regulatory status of dyes, coloring agents, and preservatives varies from country to country. Formulations of investigational drugs and PCDs must be examined carefully when preparing clinical trial materials for multinational studies to ensure that use of any of these agents is allowed in the countries where the clinical study will be conducted. For excipients that may have different specifications in specific geographic areas (e.g., U.S.P., B.P., E.P., J.P.), it is not usually necessary to meet each set of specifications as long as the regulatory submission identifies the official standard, and the dosage form is bioequivalent.

3. Regulatory Status of Positive Control Drug

When considering the PCD for a multinational study, the regulatory status of the PCD in each study country must be considered. In the United States, for example, use of an unapproved PCD in a clinical study will not normally be allowed. This may affect the choice of the PCD from one country to another.

4. Marketing Considerations

As stated in the introduction of this chapter, one of the reasons for performing comparative double-blind studies is to demonstrate health economic advantages for the study drug. The market share for a specific drug may vary significantly from one country to another, thus affecting the choice of PCD used.

Normally, it is desirable to use the market leader in each country as the PCD in a clinical study.

III. REQUESTING OR SUPPLYING POSITIVE CONTROL DRUGS BETWEEN FIRMS

This method of obtaining a PCD is used sporadically in Europe and the Americas. In Japan, however, the government encourages firms to sell blinded PCDs to competitors to facilitate the unbiased evaluation of an new drug, because the studies are normally required by the Japanese government for registration.

PCDs obtained from another company will seldom resemble the investigational drug. Thus, it is common to obtain both active and matching placebo dosage form and conduct the study using the "double dummy" method. If obtaining a positive control drug from the innovator or another firm that markets the drug, there are certain requirements, as well as positive and negative aspects for both the requestor and supplier.

A. Advantages

For the requestor, when using this method it is not necessary to develop a formulation and analytical methods. It would not be necessary to perform a bioequivalency study. Regulatory issues are also more easily resolved with cooperation from a firm that markets the formulation.

There are advantages for the supplier of positive control drug, as well. The supplier can be assured that its dosage form if fully potent and stable, ensuring optimum efficacy for the PCD in the clinical study. Commonly used agreements also allow for prior review of the study protocol by the supplier, which can ensure that the study is objective and a fair comparison, and that the PCD is administered in the correct dose and at the proper intervals. An agreement can also stipulate that the requestor will reciprocate and provide PCD to the supplier if requested.

B. Disadvantages

The primary disadvantage for the requestor is the potential loss of control over the timetable for a clinical study. Even in Japan, where the government requires firms to sell PCDs for clinical studies, there is no specific timetable for this. It may take 6 to 9 months or longer to complete all the arrangements and receive the positive control dosage form and placebo. It is important for the requestor to evaluate this timetable versus developing its own formulation, analytical methods, and regulatory submissions. Most firms supplying positive control drugs will require a copy of the clinical study protocol to ensure appropriate use of the drug. This requirement may give the supplier proprietary information regarding the requestor's investigational drug.

For the supplier, the chief disadvantages of this method are the use of scarce manufacturing, analytical and administrative resources, which may detract from research and development of the supplier's own investigational drugs. Some individuals may feel that it is inappropriate to assist a potential competitor by supplying a PCD. It is important to weigh this potential disadvantage against the advantage of a reciprocal agreement to obtain PCD products from the requestor.

C. Agreement Form

To protect the rights of both the requestor and supplier and to eliminate misunderstanding, it is appropriate to execute a written agreement between the parties. Some of the common elements and requirements specified in such an agreement are:

- Confidentiality
- Hold harmless clause
- Certificate of analysis for PCD
- Regulatory letter*
- Reciprocity
- Supply of analytical reference standard
- Assurance of regulatory compliance
- Limitation on use of PCD
- Review of study protocol
- Delivery timetable
- Payment details
- Supply of assay methods
- Adverse effect notification
- Material safety data sheet

The requestor should be prepared to supply the following information to the supplier:

- Drug name
- Size, shape, color, etc.
- Quantity (including overage)
- Total duration of study
- Description of packaging
- Dosage form
- Potency
- Date needed
- Countries where study will occur

D. Process for Obtaining Positive Control Drug

The overall process of obtaining a positive control drug from another organization will vary from case to case, but following is a general overview of the process:

1. General agreement between the parties
2. Review and acceptance of the protocol by the supplier
3. Determination of quantities and remuneration

*The supplier sends a letter to the regulatory agency authorizing the agency to reference the supplier's submission for manufacturing and control data on behalf of the requestor for the particular clinical study.

4. Timetable for delivery agreed upon
5. Purchase order sent to supplier by requestor
6. Dosage form manufactured by supplier
7. Dosage form tested and released by supplier
8. Certificate of Analysis sent to requestor by supplier
9. Regulatory letter sent to regulatory agency by supplier
10. Invoice sent to requestor by supplier
11. Requestor sends payment to supplier

As pharmaceutical products and dosage forms become more sophisticated, it will become increasingly difficult for organizations conducting clinical studies to prepare their own positive control drugs. As this occurs, obtaining PCDs from another organization is likely to become more common. It will be more important than ever to have good planning and effective policies to deal with the contingencies described here.

IV. NONFORMULATION RELATED BLINDING ISSUES

Often the blinding of clinical supplies cannot be accomplished through the manufacture of formulations. An investigational drug may be under study because its advantage over a marketed product is the frequency of the dosing interval. An example would be an investigational drug that is to be taken twice a day versus a marketed product that is taken four times a day to be effective. One method of blinding clinical supplies for a clinical study comparing these drugs would require a double dummy technique rather than look-alike formulations. For such a study, a placebo to match the marketed drug would be required. Likewise, a placebo to match the investigational drug would be required. Following is a summary of the package design:

Anticipated start date: (Month, Day, Year)
Duration of Study: 1 month
Patient duration: 30 days
Anticipated finish date: (Month, Day, Year)
No. subjects: 150
No. centers: 1 center
Enrollment rate = 150 per month/center
Initial packaging: Entire study
Drugs: Investigational drug–Viewall
Placebo to match Viewall
Dose: 1 tablet twice daily
Marketed (competitor's drug)—Markall
Placebo to match Markall
Dose: 1 tablet four times daily

Packaging

Treatment Group	Drug			
	Markall	Placebo to match Markall	Viewall	Placebo to match Viewall
Markall	150 subj/ctr × 1 ctr × 4 tablets/ day × 30 days = 18,000 tablets			150 subj/ctr ×1 ctr × 2 tablet/ day × 30 days = 9000 tablets
Viewall		150 subj/ctr × 1 ctr × 4 tablets per day × 30 days = 18,000 tablets	150 subj/ctr × 1 ctr × 2 tablets per day × 30 days = 9000 tablets	
Totals	18,000 tablets	18,000 tablets	9000 tablets	9000 tablets

Assembly: All drugs are tablets packaged in a blister card.
Blister card will be in a box.
Double blind label will be on box.

Treatment Group	8 AM	12 PM	4 PM	8 PM
Markall	M	M	M	M
	VP	B	VP	B
Viewall	MP	MP	MP	MP
	V	B	V	B

M = Markall, MP = Placebo to match Markall, V = Viewall, VP = Placebo to match Viewall, B = Blank or no cavity in blister).

Another method of blinding would require overencapsulation of both the marketed and the investigational drugs so that they look alike. Using the preceding example, the blinding for the individuals assigned to Viewall would involve the use of two active investigational dosage units and two placebo

dosage units, whereas the blinding for the individuals assigned to Markall would involve the use of four active marketed dosage units. Thus the final blister card is four cavities per day, with the subject taking one capsule per dose, instead of two tablets at two doses per day and one tablet at the other two doses.

Treatment Group	8 AM	12 PM	4 PM	8 PM
Markall	M	M	M	M
Viewall	V	P	V	P

In blind clinical trials, whether the example used above or a double blind parallel group (active versus placebo) trial, the packaging and labeling is important to maintain the blind. The external appearance of the clinical supplies for the individuals in all treatment groups must be identical. Thus care is required when selecting the various packaging components, from the immediate package holding the dosage forms, to the outer package holding the immediate package.

If the market leader, against which a company's investigational drug is being studied, is a nonsolid product, repackaging of the marketed product may not be feasible. For example, in the handling of sterile products, it may not be desirable to affect the packaging. In such cases, third party blinding would be used. This involves a person at the investigator's site who knows which subject is to receive a given drug. This person will perform the drug dispensing or administration to maintain the blind. Often an opaque sleeve or even aluminum foil will be used to wrap an IV container. If the drug is to be drawn into a syringe for administration this will be performed by the third party.

For topical, nonsterile oral liquid or inhalation products, the blinding techniques are more challenging. Although the decision must be based on the individual circumstances, a few examples may stimulate thoughts on how to package. For topical creams or ointments, one company mentioned, during a recent workshop discussion, using an overwrapped tube on the marketed product so that it looks like the investigational drug. If time allows, packaging components identical to the marketed product can be sourced. When this is done, stability testing of the investigational drug in the new components must be considered.

In studies that require only the outer package to look alike, repackaging the marketed product into a similar package to the investigational drug may be undesireable. The visible labeling must be the same for all individuals. This is accomplished by the use of open label and blind label text. The blind label text discloses the product identity and is used only if necessary. Traditionally, the open label text is affixed to the container that will be dispensed by the inves-

tigator to the individual participating in the study. This text will contain an identifying number that is unique for the participating individual, dosing instructions, the sponsoring company name and address; if an Investigational New Drug (IND) study, the federal caution statement required for clinical studies performed under the IND (Caution: New Drug, Limited to Investigational Use); if a non-IND study, a statement that the supplies are for use in a Clinical Trial; storage and handling conditions and any other unique information that will assist in dispensing, administering or tracking the drugs such as Visit or Period number at which the medication is to be dispensed.

The storage and handling conditions pose a problem when comparing two drugs that may not be stored at the same temperature. If the temperature range of one product is narrower than the range of the other, the narrower range should be used. If the ranges do not overlap, the investigational drug should be tested under the range specified for the marketed comparative drug.

V. CLINICAL SUPPLY DESIGN TEAM

When the time comes in the development cycle to think about the clinical supplies for a compound and/or specific protocol(s), a number of disciplines need to be involved. To ensure communication across the various disciplines, it may be best to form a clinical supply design team (CSDT) with representatives from such disciplines as Regulatory, Project Planning, Strategic Marketing, Operations (the commercial manufacturing unit), Analytical Chemistry, and Biostatistics. The structure of the company will dictate who should be represented. Although this often resembles the Project Team, whose responsibility it is to oversee the entire program for a compound, it differs in that its only concern is the clinical supply aspects of the project and most specifically the clinical supplies required for a specific protocol.

The CSDT should be led by the Clinical Supply Unit because this is the area in which the main thrust of preparing and shipping of supplies will occur. The Clinical Supply Unit may be represented by both the manufacturing and the packaging units or by an individual who would represent both. The responsibility of these individuals is to ensure that information is obtained from the appropriate disciplines as to proper labeling for the supplies as well as proper packaging components. This team should decide what testing, if any, is required and timelines for each discipline to complete its tasks.

The Clinical Supply Unit will draw on its experience to advise the Clinical Research Department as to package and label design. It is well equipped to perform this duty, as it works with a number of clinical research groups and thus has background for packaging various studies. In addition, it has the expertise for formulations and packagings at its disposal.

The CSDT should be formed as early as possible in the process. It is never too early. Many things need to be considered and placed into the timelines including manufacturing of unique dosage forms, obtaining comparator products, packaging components, and label stock. The earlier these items can be identified and timelines established for each, the sooner everyone will know when the study can start.

During discussions around the clinical study, a series of questions encompassing who, when, where, and how the study will be performed must be addressed. These will then be used to plan the scheduling, packaging, labeling, and assembly of the clinical supplies. The following questions should be considered. This list is only an example; each company's organizational structure and procedures may necessitate other questions being asked. The questions are based on what is important in determining timelines for processing clinical supplies.

- When is the study scheduled to start? (This will dictate when the drug is needed at the site(s).)
- How long will each subject be on study medication?
- What is the frequency of visits? (This will be used to determine the best packaging configuration(s).)
- When will the study be completed?
- How many subjects are needed to complete the study? How many subject supplies will be packaged? How many centers will be involved?
- What is the anticipated enrollment rate?
- Should all supplies be packaged at one time? (although this is desireable, because of drug availability or expiration date it may not be feasible.) If not, when is the initial packaging and each subsequent packaging needed?
- What drugs are involved?
- What is the dosing of each drug? (How often is the drug to be taken and how much of the drug is to be taken?)
- How much of each drug is needed for each packaging interval?
- What is the package to consist of (i.e. HDPE bottle, PVC blister etc.)?
- What the package configurations are to be used?

VI. CONTROL OF CLINICAL DRUG PRODUCT DURING PROCESSING

The controls used during the manufacturing and packaging of clinical supplies follow the same general rules as commercial pharmaceuticals. Current good manufacturing practices (cGMPs) must be followed. Proper segregation of all components is absolutely necessary; each significant step must be double checked, every step must be properly documented, and everything must be

adequately labeled. However, because there are actives and placebos that look identical as well as certain labeling that looks alike for actives, placebos, and market product used in clinical trials, additional controls must be used. Further complications exist when, for many protocols, the package design indicates multiple drugs in one package, whether it is a blister card with different drugs or a patient kit that contains multiple containers, each containing different drugs.

Following cGMPs, the rules for manufacture of clinical supplies are quite simple—one step at a time. During manufacture of a placebo and multiple strengths of a given drug product, a common rule to follow is ascending strengths. The placebo should be manufactured first, followed by the lowest strength of the active product. Each strength of active product would then be manufactured in ascending order of strength.

Packaging of actives and placebos is complicated by the fact that placebo and each active may look alike. Packaging documentation must be very specific for the drug being packaged. To ensure that the proper drug is being processed, only one unpackaged drug is allowed in the packaging room at a time. Each step to be followed during the packaging must be documented in great detail. Because each protocol may require a unique package configuration, the preparation of the packaging documentation is critical and time consuming. It should not be taken lightly because it will ensure quality packaging of the clinical supplies.

Before packaging commences, two individuals must verify that before bringing the drug in, everything from the prvious packaging is removed. This is critical because if a placebo for the study remains in the packaging equipment and is accidently packaged with the actives, the results of the study could be adversely affected. It is unlike commercial products, which have different appearances. Because the drugs appearances are the same, this problem may never be caught, resulting in a promising drug never being marketed because a placebo was accidently packaged as an active. Thus the clinical study results would indicate that the product did not act as expected.

The labeling presents another challenge. In blinded trials, the open label text will be identical for each drug and/or treatment group in the trial. The only difference will be the randomized code assigned to each subject in the study. This code will appear on the label and must be verified against a certified copy of the original randomization code list at the time of label application.

Depending on the type of blind label used, the product name and lot number will be visible at some point during the label preparation and/or labeling procedure. Just before this information is enclosed in a blinded fashion, two individuals should verify that the correct drug is used for the correct randomized code. Again, if this is not performed correctly, the placebo could be mistakenly labeled as the active, leading to error.

With the additional checks that need to be used in the packaging and labeling process, the time required for packaging will be significantly extended.

Another factor is time required for identification testing to verify that the packaging was performed correctly. As studies become more complicated, so does the packaging and testing. For example, a study may involve an early titration dose regimen. Such a dose occurs when an individual has to build a tolerance to a very potent drug, such as a stimulant or depressant. In such a case, the dosing will begin with a low dose and escalate up to the desired or perhaps the highest tolerated dose. As in other blind studies, each strength of drug must look alike. To ensure the proper strength is taken at the proper time, it may be desirable to package the study in blistercards, which can be labeled with specific directions instructing the subject when to take each dose. To verify that the proper drug has been placed in the appropriate blister cavity, adequate sampling must be performed. The number of blistercards to be sampled is determined by the CSDT. The CSDT must also determine if each blister cavity needs to be tested. If each cavity is not to be tested, the rationale must be agreed upon for which cavities are to be tested.

These factors cannot be overlooked. Because of the complexity often involved in clinical trials and the associated clinical supplies, planning is critical. When proper planning does not occur, either something will happen during the packaging that will cause significant delays in the availability of the supplies, or while the study is being performed it may be discovered that the supplies are incorrect. In either situation, the time lost and time involved will far exceed the amount of time required for proper planning.

VII. CONCLUSION

This chapter has defined blinding, discussed the types of blinding, and examined reasons why blinding is used in clinical studies. The primary reason for blinding is to prevent bias in the interpretation of study results. Clinical studies can be blinded by ensuring that the dosage forms, quantity and timing of dosing, packaging, and labeling are all identical. Alternatively, clinical studies can be blinded by use of an unblinded third party at the study site to dispense the study drugs and dose the patients.

We wish to emphasize the importance of PCDs in conducting double blind studies. These give clinicians a baseline against which to measure the safety and efficacy of the investigational drugs. Preparing PCD clinical materials, however, requires significant planning, can involve length timetables, and often results in extensive use of human and financial resources. The negative aspects can sometimes be minimized by gaining the cooperation of a company that manufactures and markets the PCD. Each clinical study can present unique

issues; thus the method of obtaining the PCD is best determined on a case by case basis.

To avoid unpleasant surprises in the manufacture, packaging, and labeling of clinical materials, it is critical to have good planning. This is often accomplished through a multidisciplinary team comprised of all parties who are directly concerned with the clinical materials. The exact structure of the team will depend on the organization of the company, university, or other group sponsoring the clinical study but will normally include the following disciplines: clinical manufacturing, clinical packaging and labeling, analytical testing, quality assurance, project management, and medical. A clear, well-defined study design is required to properly plan for the clinical materials.

Although science and creativity are important factors in designing and preparing blinded clinical materials that meet the needs of the study, the paramount concern must be quality. Because all materials in a double-blind clinical study look alike, it becomes absolutely critical to have excellent, up-to-date procedures for the manufacturing, packaging, labeling, and testing of the materials. GMPs must be adhered to completely primarily to ensure the safety of the patients enrolled in clinical studies but also to comply with laws and regulations. To ensure full compliance with the laws and regulations of the country in which a clinical study will be conducted, it is important to identify the countries early on, in order to plan for any unique national requirements.

The blinding of clinical materials is partly art as well as science. It requires creative and open thinking combined with excellent technical and scientific knowledge.

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Application of Computers in the Production and Control of Clinical Trial Supplies

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I. INTRODUCTION

Computer systems used in the production and control of clinical trial (CT) supplies offer many advantages over nonautomated approaches and increasingly provide means for improving the efficiency and productivity within clinical trial production units. Preparation of clinical trial supplies is an information intensive process in which the documentation resulting from a production run is as important as the physical supplies products. Documentation is the primary historical link that regulatory authorities use to judge the acceptability of clinical products and formulations. Achieving adequate documentation requires various types of information to be gathered before, during, and after an actual product is made. Computer systems not only provide efficient means of meeting documentation requirements, but they also enable real-time control of manufacturing processes and exchange of information with other electronic systems,

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such as control of laboratory instrumentation, laboratory information management systems (LIMS), supervisory control and data acquisition (SCADA) of manufacturing equipment and production facilities, human-machine interfaces (HMI) that serve as a graphic representation of production processes, material resource planning systems (MRP II), statistical process control programs (SPC), electronic batch records (EBR), and manufacturing execution systems (MES).

Systems used within clinical trial supply units touch on many classes of computer hardware and software. Typical activities performed by clinical supply units and the classes of application software used to support these processes are presented in Fig. 1. Owing to the complexity of the subject, this chapter presents only a general discussion of the different types of computer systems. It begins by outlining the clinical supply preparation process and the types of computer systems used.

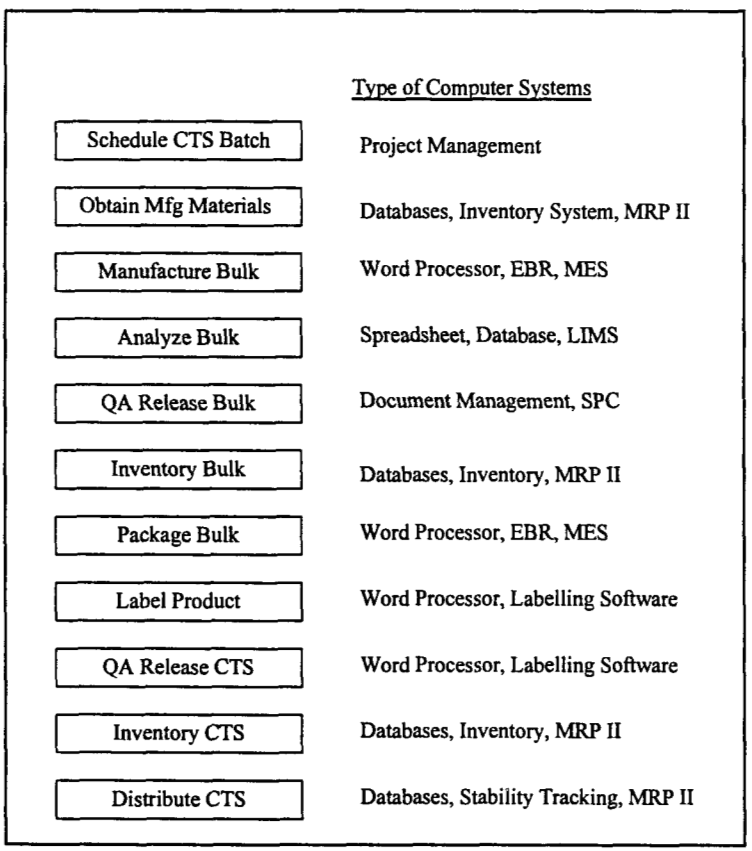

FIG. 1. Activities performed by a clinical supplies unit are listed on the left in top-down order. Computer applications applicable for each activity are listed to the right.

II. OVERVIEW OF THE CLINICAL SUPPLY PREPARATION

In general, the process of preparing clinical trial supplies begins when a customer (e.g., clinical investigator) places an order with the CT unit to supply a particular study or group of studies. Orders normally include customer requirements about dosage strength, formulation types, unit quantity, and required delivery dates. Based on this information, the CT unit plans a manufacturing campaign.

Planning a manufacturing campaign can become very involved because of the number and interrelationship of activities and personnel engaged in a project. To help manage the various aspects of the manufacturing campaign, project management software is used to automate the planning process. This type of application software enables planners to break down the overall production process into individual activities. This allows the planner to better estimate duration, resources, schedule start/finish dates, costs, and other related project information needed to successfully fulfill the manufacturing campaign. Using project management software, the planner can better compare various execution schemes to determine the best approach to achieving project commitments.

After completing an initial schedule, the planner assigns the timeline parameters as a set reference point. This set point, referred to as the baseline schedule, is stored in the computer allowing him/her to compare the proposed plans to actual executed activities. This permits the planner to extrapolate the progress of the project and reallocate resources and schedules as necessary using numerical methods incorporated in the project management software. This software tool also enables evaluating the impact of an individual project on the schedule of other projects sharing the same resources. By using computerized project management techniques, reports can readily be generated, revised, and distributed among participants using electronic mail. This is an efficient tool to communicate current information to individuals throughout an organization and provides a consistent mechanism for presenting reports on an ongoing basis.

Access to project information, such as availability of excipients, active drug substance packaging components, and suitable formulations, is necessary to progress the manufacturing campaign. Depending on the organization, this information may exist in different locations and formats ranging from handwritten laboratory notebooks to an all inclusive information management system. Good manufacturing practices (GMP) require information relating to raw materials and packaging components be accurately documented using a scheme defined in a standard operating procedure (SOP). Most companies will use a computerized inventory management system to achieve this goal. The inventory management system relies on a database to track receipt and transfer of materials, maintain reorder and expiration data information, as well as manufacturer and supplier data. Inventory systems can be as simple as a multipage

index file to as complex as a material resource planning system that integrates production schedules with material allocation and disposition.

Other information is needed to document a manufacturing campaign and may include databases on formulation composition, certificates of analysis, material safety data sheets, product specifications, and training records. All excipients, packaging, and bulk drug are required by GMPs to be released by a quality control group. Tracking all the testing schedules for these materials can become extensive. Testing schemes conducted by a quality control group is another database that often is used. This application may exist as a stand-alone program, such as personal computer-based project management software, or may be part of a larger LIMS maintained on a central computer.

After the bulk materials are tested and found to meet specifications, either internal or the supplier's, the approved items are suitably labeled. Labeling of the materials may use a simple system such as preprinted labels upon which handwritten information is added or more elegant approaches that use an inventory database to generate labels with product identification codes and bar code symbology for automated data entry. After the materials are labeled and released, they are moved from a designated quarantine area into a section designated for released goods.

When a manufacturing campaign begins, excipients, active ingredients, and packaging components are allocated and reserved. Needed processing equipment and manufacturing areas are also scheduled. The reservation mechanism used by the CT unit may range from a simple chalkboard listing the relevant information to specialized manufacturing software. Depending on the level of computerization, this software may be a stand-alone application on a single personal computer or might be a module in a larger integrated system used to manage the overall production schedule, such as an MRP system.

The central element used to document a production run is the batch record. Production batch records guide an operator in the processing of the batch and document the actual events that took place during the run. Batch records list the formulation, quantity of materials, processing procedures, and any other pertinent information such as relevant equations or look up tables. Batch records take on different appearances depending on the type of product, policies within an organization, and the amount of automation. In a rudimentary system, information is recorded manually, attested to with a signature and verified by a second worker. Changes made to the batch record are required by GMPs to be neatly crossed out and any new information written on the document accompanied by the person's initials and date. External data, such as recorder output, are either written directly onto the batch record or appended to the document.

In contrast, batch records take a different role when used in an automated system. In the extreme case of a completely electronic batch recording system,

all events are documented through electronic exchange between interfaced equipment and computers with operator interactions entered via a connected terminal. When an electronic system is used to prepare batch documentation, it is important to adequately protect records to prevent the electronic files from being inappropriately altered. Therefore, it is important that such systems have secured audit tracking capabilities, which are procedures that ensure all interactions with the system are first authorized before being carried out and then recorded permanently in an operations log.

Manufacturing campaigns vary depending on the formulation, processing complexity, and batch size. Manufacture of clinical trial supplies can range from a completely manual operation on a small batch (e.g., hand mixed and filled) to a fully automated operation using commercial production lines. During an operation, real-time data may be obtained from the processing equipment. Real-time data may be used to control processing parameters or simply to monitor and document the manufacturing run. Product samples may be taken for in-process testing to help adjust parameters of an ongoing process or to document events during the manufacturing campaign.

When automated control systems are extensively used, such as with MES, the production process is regulated primarily by the computer rather than an operator. In these cases, application code is written specifically for each production step. This code specifies the equipment, formulation, materials, and all processing events and triggers. Because the computer regulates and records all activities, every possible event must be considered and programmatically handled. In an R&D environment, this may be difficult because of the limited experience with the product and process and the limited time or capability to suitably test the operational code before running the batch. For these reasons, few CT units use automated manufacturing execution systems and, instead, rely on manual or semimanual documentation methods.

After completing bulk manufacture of CT supplies, the product is placed into quarantine, and samples are taken and submitted for release testing purposes. Analytical testing of the materials is performed to evaluate whether the materials meet predefined specifications. Test specification methods and results can be stored in LIMS.

There are normally several computer systems in an analytical laboratory. Most instruments are interfaced to personal computers or have built-in microprocessor controllers. Often personal computers are dedicated to an instrument to record, analyze, and display information from only that unit. In other cases, several instruments may be connected to data acquisition modules that transmit digitized signals to a centralized computer system that simultaneously manages the input/output from the equipment.

Information relevant to the bulk manufacturing process is reviewed, and a decision is made to release or reject the bulk product before transferring the

material out of quarantine. On release of the bulk materials, they are transferred from the quarantine area to the released goods area and suitably labeled.

At the appropriate time, the clinical trial supplies are packaged. Suitable batch records are prepared based on the customer requirements for packaging and labeling. Packaging of clinical supplies often cannot be automated because of packaging requirements necessary for blinded studies. Packaging batch records, like manufacturing batch records, are normally created using word processors. Standard document formats are used to maintain consistency between batch records. These templates may consist of standard formats for data entry and signature lines. Approved phrases and methods descriptions may also be stored in the word processor, allowing an author to pick the desired text from an existing list. Word processors also provide cutting and pasting, enabling existing documents to serve as a template for newly created documents.

Packaging and labeling requirements for CT supplies are often unique to an individual study. The process is started by preparing prototype labels. This may require the use of graphic design programs or computer assisted design/computer assisted manufacture (CAD/CAM) systems to achieve the spatial dimensions needed to generate the label layout. After the label is designed and prototypes prepared, these are submitted for approval to the customer or regulatory representative.

Preparing labels for CT supplies can be complex because of the need to have individualized labels listing the correct patient identification information and the physical printing of the labels. Mechanically printing and assembling CT supplies can be complicated because it needs to adequately identify the package during assembly, then be altered to blind the supplies for patient use during the study. The label on the package must also be able to be unblinded in case of an emergency.

After approval, the labels are generated with the appropriate information (e.g., protocol number, site identification, patient number, instructions for use, randomization code). The bulk product is then packaged into suitable containers and labeled for patient use. After completing the batch, the finished goods are placed in quarantine, and appropriate batch records are judged as to whether to release the product. Once approved, the batch records are archived. The completed clinical trial supplies are placed into inventory ready for shipment to study centers.

When appropriate, the finished product is dispatched to the study center, and records of the dispatched CT supplies are recorded in a log or database. The information is necessary to maintain the usage and location of the drug product in case of recall. These same records may latter be appended to include information about returned goods needed for product reconciliation purposes. In addition, some of the finished product is placed on stability for the term of the study and periodically tested on a prearranged schedule to check that the

CT materials meet necessary specifications. A database of the stability testing schedule is used to manage the testing by quality control laboratories, which is necessary to ensure the drug product is within specifications while the supplies are used in the clinic.

III. DIFFERENCES BETWEEN COMMERCIAL AND R&D APPROACHES

This overview creates a framework to discuss the different types of computer applications used in clinical trial units. In many ways, the procedures and methods for preparing clinical trial supplies are similar to those found in commercial production; however, there are also fundamental differences. In commercial manufacturing, production runs are operated with the goal of having each batch made identically to the previous ones, while aiming for maximum productivity and minimum cost. In contrast, CT units work with limited information about formulation and manufacturing characteristics of the batch. Batches are generally smaller than commercial scale and often changes as the process is scaled up from research to commercial scales, causing the process to behave differently at each batch size.

Productivity and cost containment are less of a factor in CT units than in commercial production. Because of the limited knowledge about the product characteristics, the process used to make CT supplies must be flexible to avoid potential problems and maximize the probability of successfully completing the run.

Differences between R&D and commercial processes also lie in the type and quantity of the information gathered. Knowledge collected for the CT supplies is used to guide future production trials, support regulatory filings (i.e., New Drug Application [NDA], PLA), and support preapproval inspection audits to confirm that the supplies were suitably made and adhere to the claims in the clinical protocols. In contrast, information from commercial manufacturing environments is used to maintain on-going product sales, provide supporting data for routine regulatory audits, and protect against product liability suits.

Commercial manufacturing groups use various strategies to maximize productivity, such as using automated production processes to reduce labor costs, using MRP systems to minimize inventory holding costs, and integrated information management systems to speed workflow while reducing slack time. Although effective in improving commercial manufacturing, these approaches are less applicable to the R&D community because of the reasons stated earlier.

Many computer applications needed by CT units have limited applicable outside this user community. Specialized software needed by CT units often is not commercially available, requiring applications to be specifically written or

significantly altered from available commercial products. For these reasons, selection and implementation of computerized systems for CT units have to be carefully evaluated to ensure that the application meets the user requirements in a timely, regulatory, compliant and cost-effective manner.

Preparation of clinical trial supplies is an information intensive process, which requires reliable information storage and retrieval. For this reason many CT computer applications rely on database management (DBMS) systems.

When a database is intended to be a stand-alone application, development of the program can be written without concern over exchange of information between databases or other applications. However, if the application is required to exchange information with separate systems, either existing or planned programs, the writing of the application is much more difficult.

Devising applications that effectively integrate multiple databases yields the productivity and cost reduction benefits, such as found in commercial MRP and MES programs. The small market size, lack of standards, and regulatory requirements have thus far prevented such integrated systems from being readily used in the CT unit arena. There are no standard programming conventions, database structures or schema, or other software product conventions, and because no products in the CT area are dominant, there are no ad-hoc standards.

Many classes of information are involved in the preparation of clinical trial supplies. Most of these are required by GMP. Database applications are best suited to handle the storage and retrieval of information. The classes of information are the following:

- Raw materials and component inventory: track disposition of materials used in the manufacture of clinical trial supplies
- Equipment and room logs: list the equipment and room logs usage by person and material processed; also provides a history of the cleaning of the equipment and rooms
- Training records: records the training history of the staff usually in context of an SOP or specialized training (e.g., respiratory training, forklift operations)
- Product specifications: technical specifications on the product and package to judge the product for initial release, guidelines for storage, and life of product requirements
- Test procedures: instructions about testing (analytical chemistry and microbiological) of the product for quality assurance purposes
- Test results: repository of test reports used for tracking the stability of the product and trending variation between manufactured batches of the product
- Batch and labeling records: archive of the production batch and packaging records, either approved before use, used in the actual production, or both
- Clinical supplies inventory: physical inventory information on released

products and the disposition (i.e., what materials were sent to which clinical site and when)
- SOP records: copies of the currently used standard operating procedures and details of historical changes to the SOPs

A primary consideration in any computerized production and control system is that it complies with good laboratory practices (GLP) and/or GMP guidelines. The most basic of these requirements is that the system be validated. Validation refers to the formal procedure of verifying that a combination of computer hardware, application software, and interfaced equipment performs a defined operation under specified conditions. To achieve this requires that:

1. The scope of the process/task be defined
2. A suitable operating procedure written
3. A plan is written to adequately test the procedure
4. The prescribed testing plan is performed and completely documented
5. In normal use situations, the operator follows the written operating procedures.

Historically, most large CT computer applications such as inventory and clinical labeling systems were developed and operated in a centralized mode using mainframe or large mini-computers. Computer resources such as programmers and available processing time on central computers were limited. Only applications with clearly defined goals and high cost/benefit ratios were implemented. Few applications were available for the specialized needs of the CT unit, so either the required programs had to be custom written or commercially available software had to be extensively modified.

As computer technology advanced, more and more applications were ported over to mini-computers, workstations, and personal computers. With increasing market size, the number and variety of applications available grew. In addition, the tools available to programmers also improved, thus enabling programs to be written better and faster. As the cost of computer time decreased and the number of computer users increased, programs used improved user interfaces, and computer applications migrated away from centralized mainframe environments to distributed environments on local area networks. Rather than perform all the application processing on a central computer, such as database management programs, distributed computers accomplish a greater role using such approaches as client/server and file server technology.

IV. POTENTIAL VALUE VERSUS ACTUAL DELIVERY OF COMPUTER SYSTEMS

The advent of computers has increased productivity in the domain of clinical trial supplies; however, the potential of computers far outweighs the actual

delivery of useful computer applications. Why is this? Each year computers and computer software seem to be getting less expensive while the computing power is dramatically advancing. Why is it that CT units cannot get the computer systems and applications that is needed? To answer these questions, we need to understand the issues surrounding the field of computers in the pharmaceutical R&D in general and the specialized area of clinical trials supply preparation specifically.

Computer technology is rapidly advancing driven by the marketplace and the ability to sell new and improved hardware and software to an ever expanding computer user base. The pharmaceutical industry is an important market segment for the computer industry because it represents a business that relies on keeping technologically current and spends a large proportion of the corporate budget on funding R&D and capital equipment (e.g., automated instruments and manufacturing equipment, specialized scientific software, faster computers). Many computer vendors are vying for a share of this lucrative market. This would suggest that many potential hardware and software solutions are available.

The population of potential users within the clinical trial supply arena numbers only in the thousands. Each CT department within a company requires both general purpose computer applications (e.g., word processors, spreadsheets, databases) and several highly specific applications (e.g., stability systems, bulk chemical and packaging inventory, labeling systems). The computer industry thoroughly serves the general purpose user, whereas in the area of CT supplies much fewer vendors are operating in this small market.

Owing to the specialized need of the users within the clinical trial supply domain selecting, justifying and implementing new application software and/or computer hardware can be challenging. Creating viable solutions to clinical trial supply problems requires a thorough understanding of the business process and the potential impact of the solution. Solutions based on computer applications can only provide a tool to assist, improve, or augment the business process. The functional benefits of the technology has to be accessed in a realistic, quantifiable manner. Unfortunately investigating what and how new technologies can be used is a time-consuming task. The clinical trial supply manager may not have the available time to investigate the various options or may not have the technological knowledge necessary to evaluate the choices. Often the task of locating and implementing new technologies is relegated to so-called technical specialists, who may understand the technologies involved but often do not have insight into the business process. Consequently, major decisions affecting business strategies are made at lower organizational levels by managers who may not have the strategic perspective necessary to evaluate such

decisions and thus adopt narrow, short-term perspectives seeking easy solutions that may not integrate with other business systems.

Several products may be available to enhance automation and information technology, but these product vendors provide a standard product, also referred to as shrink-wrap solution. These products have the necessary elements for the application; however, most require a degree of customization for the application to be deemed worthwhile. The level of customization has major shortcomings with regard to implementing new technologies. Implementing new technologies requires a set of documentation, which include user requirements, system specifications, detailed designs, vendor audit reports, validation protocols, user manuals, and SOPs. Generating these is a major component in any new computer systems in the clinical trial supplies domain. These documents can be generated by any number of sources such as clinical trial supplies staff, product vendor, in-house information technologies specialists, hired system integrators, or independent consultants. Regardless of the source, generating the necessary documentation is a time-consuming and sometimes complex task. The task can be challenging because clinical trial supplies automation or software application projects are a highly specialized endeavor that serves a small user base.

Another issue with any new computer application is whether the new system will be a stand-alone unit or integrated into an existing information technology infrastructure. Many clinical trial supplies functions require communication with other units within the clinical trial supplies unit and outside it, such as to the regulatory, clinical departments, or manufacturing departments. Most groups that interface to the clinical trial supplies unit have their own information management systems, which often have custom developed applications. Developing communication links to these existing systems can be difficult because of differences in communication protocols, differences in data objects and their meanings, and issues surrounding read/write/delete privileges. To achieve success on larger integrated computer solutions, a team approach is normally used to integrate technology, business process, and regulatory aspects of the project. Often these integrated projects threaten functional managers who may not be committed to the project. Many of these larger resource intensive computer projects focus on labor and personnel cost-cutting rather than quality improvement or cycle time.

For smaller, less strategic problems, it is often easier to use stand-alone applications rather than integrated ones because it is easier to get things done on an individual basis using personal computers than to rely on team or system specialists. The application may have only limited applicability but can get completed in a timely manner under the regulatory radar scope, thus limiting the necessary overhead needed for validation and documentation purposes.

V. EVER CHANGING TECHNOLOGY

The computer industry is rapidly changing. Faster, more powerful computers and user-friendlier computer applications are available. With all this advancement, however, the regulated portion of the pharmaceutical industry in general and clinical trial supplies domain specifically are hindered from taking advantage of these advances.

A major task within the clinical trial supplies area is the creation and retention of manufacturing batch records. These documents are critical to the preparation and quality assurance release process. This document serves as the record for the prepared clinical trial supplies. In many cases, data for batch records are generated from the computerized systems that print out the results on paper forms. These documents then are appended to the official batch records after being verified and signed by the operator. In the effort to get to a paperless environment, results from computer systems are desired to be directly incorporated into an electronic file. However, owing to several regulatory issues, the advantage to using computer systems for batch records is forfeited. For example, only recently has the issue surrounding the use and authentication of electronic signatures been defined and published by the Food & Drug Administration. Before this change, the use of electronic signatures were avoided because of the uncertainty of whether the methodology would be accepted by the FDA.

There has been much effort to replace paper documents with electronic ones. Electronic documents have many advantages over paper documents. One of the key problems with switching over to electronic media is directly attributable to the dramatic advances in computer technology. These advances help to improve the productivity and efficiency of new systems, whether they be operating systems, computer programs, new microprocessors, communication protocols, or storage media. As these technologies replace the old ones, the issue of reading retained electronic information becomes an important issue, because the new computer technologies are changing so rapidly and may not be compatible with the new systems. To avoid the issues of compatibility, it has been simplest to store official documents on paper because techniques of handling paper-based information is clearly established and will not change in the near future.

VI. FUTURE TRENDS

As society is affected by the rapidly and ever changing advances and innovations brought about by computer-based technologies, so too will the future of clinical trial supply production and control be reshaped. Many methods not considered viable today or not even imagined will quickly become routine as

a result of advances in high technological manufacturing, telemetry, data communications, and information systems. The increasingly competitive pharmaceutical marketplace is demanding that the drug development life cycle, from the discovery through product launch, be shortened and made as cost effective as possible. Achieving this goal requires that every phase of drug development do more with less and in shorter times.

Two of the most constraining factors in CT supply production today are sufficient time to manufacture and package clinical supplies and the availability of bulk drug product. Overcoming these factors requires CT units convert to just-in-time (JIT) manufacture and packaging operations. Succeeding with a JIT approach requires producing more but smaller batches in shorter time but with acceptable levels of regulatory compliance. With the shortened timelines of today, it is often not feasible to wait for release, so more and more companies are packaging and labeling "under risk' before release.

Effective integration of information technology, automation, and efficient clinical supply processes are the only means to achieving JIT. One method that may be required is individually identifying each dosage form (e.g., tablet, capsule) while maintaining product blinding to the patient and clinician. Use of digitized and/or encrypted printing (also know as branding) of individual dosage forms will be necessary. In this way, supplies could be 100% inspected by bar code scanners and certified. Laser etching or in-jet print may be used for this process. Similarly, patient packages could be individually assembled on an as needed basis rather than being produced in large quantities, as is done today. Again with machine-only readable identifiers, patient packages could be inspected by bar code scanners and documented. In this way, manually prepared documentation would be significantly reduced or avoided. In addition, extended levels of flexible automation (i.e., robotics) could be used instead of human labor because of improved verification methods.

Bar codes are beginning to be used more extensively. They have several advantages:

- Operators training files can be linked to the various steps and operations in manufacturing, packaging and labeling. Thus before someone performs an operation, he or she must be trained and the training documented; if not the system will not allow the step to be performed.
- Once an operation has begun, only the person logged onto the system can continue with each step.
- Each type of component is barcode labeled; thus there is always proof of what was used. With proper validation, only the correct components will be allowed in a packaging room.
- Only after the correct item and quantity are placed into a container is a study label printed. This ensures that only the correct items are labeled. It

also eliminates the wrong labels being brought in to the room, as labels are blank up to the point the container is labeled.

- The computer acts as the second check; thus operation can be done by one individual.
- Unless something is intentionally mislabeled in the beginning, everything is correctly labeled.
- The system can be designed so that the time required to perform each step is automatically documented. This can be used in projecting the time required to perform additional projects.

Dependable forecasting of clinical supply usage rates is also required to succeed at JIT. Most clinical trial units are unable to keep current account information on the disposition of clinical supplies in the field. Accurate and current tracking of inventory levels require on-line data collection techniques within both the clinical setting and patient's home. Simple and efficient communication links and inventory software are needed between the sponsoring company and the field. Study investigators could keep a running account of CT supplies, as well as other protocol compliance information using digital communication methods, such as the Internet or dial-up connection to the sponsor's computer network.

The Internet is an important communication tool and is becoming common in both business and residential environments. The World Wide Web (WWW) on the Internet, the multimedia interface that allows text, animation, video, and audio presentations of information, is an ideal medium for communication among the clinician, study participant, and pharmaceutical sponsor company. The WWW is well suited for interfacing to clinicians and study patients because of the ability of the web site to customize the presentation and delivery specific information to the person connected to the site. By developing a suitable web site on the WWW, the sponsoring companies can achieve results that were not feasible in the past. Examples of applications include, real-time disposition of study participants, inventory of CT supplies, and requests for additional supplies. In addition, because the Internet is available worldwide, the information maintained on one centralized web site could be used for local or international coverage.

In another approach to capturing patient use of study supplies, as well as compliance to study protocols, each patient could be supplied with a personal digital assistant (PDA) or some other type of small self-contained portable computer. This computer could be programmed to prompt the patient to take the appropriate drug or activities, certify by bar code scanner the product used, and record all other appropriate information. These data could be transmitted immediately via cellular wireless communications back to the study center or

to the pharmaceutical company sponsor. In this way, a true inventory of clinical trial supplies would be known, as well as the rate of usage. Given this feedback, effective forecasting would be available to plan and execute the preparation of supplies.

VII. CONCLUSIONS

The pharmaceutical R&D community is under pressure to reduce operating costs and speed the time to market of new drug entities or product line extensions. Although the industry is pressured to speed the development process and simultaneously maintain GMP, accurate documentation and other regulatory compliance standards cannot be jeopardized or else the submitted product may be called into question by a regulatory authority, thus delaying product approval for market introduction.

The advent of computer systems within the R&D community, and specifically the CT unit, is the most feasible method for improving the performance of the drug development process. Although often viewed as an adjunct tool helping the CT group achieve its mission, computer systems are playing an increasingly strategic role in improving the quality, reducing the cost, and speeding the preparation of clinical trial supplies.

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Total Quality Management of Clinical Trial Supplies

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I. INTRODUCTION

There is undoubtedly a big picture within the realm of clinical trials supplies (CTS) that lends itself to a total quality management (TQM) systems approach. Numerous texts, many directly or indirectly resulting from the classic works of the TQM guru William Edwards Deming, can be cited (1–6), and will form the basis for much of the thinking within this review. Although there are no publications that embody a comprehensive TQM evaluation with CTS, the application of TQM within the pharmaceutical industry has been addressed (7), and recognizes the need for flexibility, urgency, and innovation. Moreover, the relevance of TQM to the CTS process has previously been noted in a recent drug development management overview (8). In many respects, a CTS operation, even within the scope of the multinational corporation, parallels the activity of a small manufacturing enterprise. Both have (require) a structure

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(people), aim, methods, materials, equipment, and function within (and have interdependence upon) an external/internal environment. As a consequence, the reader is invited in this chapter to consider contemporary TQM systems theory publications (1–4, 9), and couple this thinking with the more tactical publications (10) on CTS. Well-known strategic approaches such as manufacturing resource planning (MRP II) and Just-in-time manufacture are also relevant considerations. TQM does require effort and resourcing, but the benefits of reviewing "not what you do, but the way you do it" can be considerable. The Japanese manufacturing industry can be cited as a well-known example.

For the purpose of this review, a TQM system can be defined as an interdependent group of items/assets, people, and processes with shared goals and a common customer focus (purpose) (11). To implement quality management and improvement as a strategy, it is essential to view a CTS organization and process as a system. This helps the component members of the organization understand the interdependencies within the organization. It also enables focus of everyone on shared aims and the needs of the external as well as internal "customers." Vital aspects for consideration within the system are structure, aim, interdependence, and quality improvement. Viewing an organization solely as independent departments (with their own hierarchies) may induce suboptimization (manifest as a lack of integration and transparency) and potential loss to all contributing within the system. There can be many other sources of suboptimization (TQM ignorance). Probably all of them are experienced at one stage or another during the evolution of a CTS organization.

Management, therefore, has the all-embracing and vital role of creating an environment conducive to system analysis, review and quality improvement. A major challenge is to accomplish this simultaneously to "just doing the job." Moreover, without the leadership to review and improve the entire system (and without the knowledge of how to make improvements), the spontaneous resort to local discrete actions that appear to induce immediate improvement may actually result in a loss to the entire system. Management must view the clinical supplies organization as a system of processes and manage the improvement of the linkage between such processes, if necessary, by removal of blockages or obstacles to the linkage. The rate of improvement is critical to success. Rapid change needs to be implemented, although this may be done (and invariably is) incrementally. Rapid learning (CTS system review) is a prerequisite to achieve expedient improvement. The Deming School (6) cites the classic chain reaction: Improved quality through improved productivity through increased competitiveness leads to return on investment. This may also be applied to CTS, where improved quality leads to increased expediency and efficiency ultimately through registration and return on investment by accelerated product launch. It is this fundamental thinking that justifies the implementation of TQM into the CTS arena.

As a final introductory note, one of the first steps in improvement of a CTS process is to discover whether the process is dominated by variation, and if so, the source and nature of this variation. Anthologies could be written on variation control and understanding. Without at least some comprehension of the root causes of variation in the clinical supplies system, improvement strategies cannot be adequately founded (9,12).

This chapter is subdivided into the major TQM component sections: customer focus, systems theory, continuous improvement and variation. However, it is important to note that TQM/CTS should be an applied philosophy, not a definitive list. Moreover, there is absolute overlap between all elements within a TQM systems approach. All such elements of the system should be implemented for it to perform as effectively as possible.

II. CUSTOMER FOCUS

The Medical Department is the obvious customer in CTS process; however it is vitally important not to consider this invariably powerful, persuasive group to be the only customer. The clinical supplies operation itself may also be considered a customer, insofar as it needs, for example, information on protocol, bulk clinical request, randomization, comparitors, shipping information, etc., from associated medical department(s). It is therefore worthwhile to establish customer/supplier chains, to define whom is dependent upon another group for critical information. A brief example of an isolated customer supplier chain is given in Table 1. There are many other such chains within the CTS

TABLE 1 An Example of Clinical Trial Supplies Customer Supplier Chain

Customer	Supplier	Summary of deliverables
Patient	Study investigator	Compliant, well-tolerated medicine, readily understood and used.
Study investigator	CTS unit/medical department (CRA)	Patient direction, training or use and/or product manipulation (e.g., reconstitution). Compliant quality supplies and investigator brochure.
CRA/medical study director	CTS unit	Accurate ship date and requested numbers of packaged supplies of adequate quality.
Shipping group	CTS packaging unit	Timely packed stock, shipping storage directions.
CTS packaging unit	CTS manufacturing unit	Timely bulk product, released to specifications of sufficient number with retest date.

process, embracing, for example, regulatory authorization, shipping, customs, senior management, comparitor agent sourcing companies, contractors, formulation development, toxicology, and process-chemistry. These chains are not isolated, but consolidate like the branches of a tree. This network constitutes the CTS system that will be discussed within the next section. Customers and suppliers can be both internal and external to the organization. One possible definition of customers is those whose ability to do their jobs depend on how well any job within the entire CTS system functions. Excipient or componentry vendors are examples of external suppliers (the CTS unit being the essential customer). It is therefore important to integrate vendor dependencies into the CTS planning and communication process.

"Everyone owns the customer" (9) is a mentality all people contributing to the CTS process should consider, thereby eliminating the "somebody else's problem" concept and focusing on true goal and achievement orientation. This also has the added benefit of even junior CTS operators, understanding that they are "not just an unimportant cog in a big wheel." Instead, the CTS patient is their customer who deserves the highest professional and ethical standards.

Customers, nevertheless, require (and even demand) management. Many people might argue that medical departments certainly do! It is frequently a sound idea to have individual(s) dedicated to customer/supplier interface management. In this way, time is allocated to essential communication, definition of critical goals, priorities, objectives, and dependencies. By way of example, a clinical supplies liaison position can be established to manage the critical interface position with such medical departments. Examples of activities of such a position might be the following:

- Track CTS status and ship date to study site, providing precise, clear updates/feedback to medical, CTS staff, and associated departments.
- Train and advise the medical customer on procedural aspects regarding supplies procurement. Also help them recognize critical dependencies and timely information requirements.
- Help consolidate bulk manufacturing requests to streamline CTS manufacturing activities and ensure efficient use of manufactured bulk product and drug substance, while anticipating overages.

Thus, the liaison position serves to assist *both* the customer and the supplier and illustrates the critical need for interface management. Absence of sound interface management can lead to miscommunication, mistrust, and ultimately breakdown of a CTS system. One could easily envision the disastrous scenario of a frustrated clinical study director repeatedly telephoning an overworked "Pharmacy Drug Store," each time speaking to someone different with a subtly different story to tell! Thus, customer-focused interface management

plays an important role in the effectiveness of customer/supplier interaction, and hence, the CTS system itself.

TQM CTS should wholeheartedly embrace the "win/win" concept. As a simple example, if a study starts according to schedule, everybody wins: the CTS department, the medical department, all associated departments, the patient, the investigator and ultimately, R&D and the company. It is important to note that a win/win mentality starts at the top of a company. Finger-pointing/assignment of blame is not a way to get the job done. It is better to recognize the need to "teach" a win/win mentality, and "enforce if possible" by "actively discouraging" those who may attempt to politically undermine this mentality. Moreover, frequently CTS is invariably an invisible operation until something goes wrong, particularly in the large corporation. It is important to judge the CTS system (if it must be judged) on the big picture of its achievements, rather than the single error or failure. However, it is equally important to note that perception plays a critical role and can be heavily influenced by the (mis)behaviour of one or more customers.

Pride is important to build as a win/win attitude in both the customer and supplier (this should not be confused with dogma). Pride in quality and the commitment to achieve customer goals may potentiate trust within the CTS operation and create a climate of cooperation. One way of potentiating this within the CTS arena is to establish customer/supplier "moral contracts." For example, state what you will do and deliver it with the highest possible quality. The Federal Express motto "underpromise and overdeliver" is frequently cited (8,13), but it is recommended that "realistically promise and absolutely deliver" is a more appropriate motto within a CTS "moral contract." Habitual "underpromise/overdeliver" could create a climate of mistrust within a cooperation (particularly the CTS/medical relationship) leading to second-guessing and/or interrogation of any "underpromised" delivery schedules. Interestingly, the teachings of W. Edwards Deming do not subscribe to the use of slogans (6). The basis of his argument is that exultation does not accomplish anything, but achievement/customer focus proves it!

As a corollary to win/win cooperation, breaking down historical barriers is vitally important. This may take active management attention on "both sides of the fence," management therefore owning the system, rather than defending a given process. Mutual contribution, not competition, should be the goal. This may also serve to potentiate groups/individuals being mutually respectful and genuinely concerned for each other, thereby fostering shared belief and trust. A final point is to drive out fear. A quality CTS system cannot be built on fear of reprisal for failure. On the contrary, if failure occurs, management becomes a customer and should be provided with an urgent action plan for

resolution of the immediate issue, an analysis of what went wrong, and proposals for future system modification to eliminate recurrence.

It is important to listen to the voice of the customer (i.e., customer feedback) and to also look at distinguishing aspects of the customer (e.g., within a given therapeutic area, or using a certain complex formulation) in the review of the CTS customer information. Various tools and performance measures (Table 2) that also may be used to obtain and assess customer feedback are discussed later in this chapter. For example, focused questionnaires and systems for detailed observation of product use and formulation can be read together with customer feedback and, in extreme circumstances, complaints. It is important that as given, for example in Table 1, patient anecdotes about formulation use or difficulties find their way back (along the often tortuous customer/supplier chain) to the responsible party. In particular, feedback to external vendors is often neglected in the pharmaceutical development area, except in acute problem circumstances, which is an important omission. Feedback should be specific, and as necessary, prompted by specific questions. Thus, an objective is to "make it easy for the customer to tell you their feelings" (facilitated by both easy communication method[s] and receptive minds). This should be coupled with hard work to neutralize dissatisfaction and, is possible, turn it into a positive experience for the customer by prompt, sincere concern that demonstrates care and commitment to resolution. Supplier management (or focus) is a prerequisite for customer focus further down the chain. Although it may be tempting to purchase inferior products to achieve expediency or save money, it may often result in problems further down the chain, and associated loss of credibility (the total cash and/or time saving being ultimately negligible). It is important to recognize total cost and work with the supplier to achieve win/win on cost/quality and timing. As an example, cheap but inferior punch tooling could compromise a tablet batch or even a machine and result in CTS disaster.

True customer focus, particularly to external customers, will help create alignment of the CTS system (i.e., all internal disciplines pulling on the same rope in the same direction). CTS systems thinking will now be discussed.

III. A CTS OPERATION IS A SYSTEM

Sandwiched between supplier inputs and customer outputs is the "system." On a macro scale, this could be the input of bulk drug substance from a process chemistry department with an output of a labeled, randomized, blister card of tablets taken at home by a patient. The CTS "system" makes it happen. On a micro scale, this could be the shipment of packed stock to a study site and its receipt. The details form the basis of the shipment "process." This shipment process may be summarized as: regulatory approval to ship, the clinical research

TABLE 2 Examples of CTS Measurement Criteria

Resources
Full-time CTS staff (per project)
Temporary staff
CTS staff/CRA ratio
Activity and/or project specific man-hours
Activity and/or project specific revenue expenditure
Capital investment budget
Training hours spent
cGMP related activities (e.g., number of SOPs in place)
SOPs revised, validation reports issued, etc.
Manufacturing
Diversity of dosage forms (equipment)
Number of units manufactured by dosage form
Project specific batches made (with placebo)
Actual yield (bulk drug overage justification)
Total number of units (by dosage form released into clinical inventory)
Contract versus in-house manufacturing activities
Failed lots (including those terminated during manufacture and reason)
Mechanical equipment repair turnaround time
Manufactured units sourced from commercial operations
Cleaning verification turnaround time
Packaging/labeling
Number of primary packs by project and/or formulation
Number of new protocols/packaging jobs
Number of long-term protocols (needing resupply)
Packaging job complexity (e.g., blisters vs. bottles vs. pre-packed samples)
Repackaging jobs necessary to support an amended protocol
Open label versus blinded studies
Total labels generated (for studies, reference samples and documentation)
Foreign language labels generated (plus approval timeline for label copy)
Contract versus in-house packaging and/or label generation activities
Failed or inadequate packaging jobs (plus reason)
Product supplied
Number of shipments
Weight of product shipped
Number (and weight) of international shipments
"Dangerous goods" shipments
Controlled drug (Drug Enforcement Agency) shipment
Phase IV versus phase I-III studies supported
Miscellaneous (e.g., breakout or concomitant medication/diluents/infusion sets/ etc.) supplies

(*continued*)

TABLE 2 Continued

Product returned
Unused drug returns from the field
Expired bulk chemical and drug product inventory
Comparitors
Blinded comparitor ex pioneer company—types sourced cost and amount
Comparitor manipulation performed (products and number of lots)
Product supplied to support comparitor reciprocation plus lead time
In-house versus contract comparitor work plus lead time
CTS cycle time and process stability (workload efficiency and complexity)
Bulk request receipt versus release into clinical inventory
Bulk manufactured product analytical/QA release turnaround time
Packaging identification analytical/QA release turnaround time
Draft versus final protocol receipt, versus ship date (plus any deviation from agreed lead time)
Incidences of unclear, inadequate requests received from customers (e.g., incomplete request paperwork)
Duration of packaging/labeling job
Completion of QA release versus actual ship date
Continuity of clinical development plan (i.e., long-term plans) versus protocol requirements (i.e., forecast accuracy)
Frequency of changes requested within an agreed frozen period
Percent supply conforming to requested ship date

associate (CRA) dispatch order, the notification of shipment, customs clearance, transport (in controlled conditions), and receipt notification at site. Thus, a CTS system is made up of numerous, interdependent processes.

Because pharmaceutical technology is an integral part of a CTS system, quality should be designed in the system (along with customer focus) to guarantee reliable and timely CTS. It is unacceptable, for example, to notice placebo tablets with black spots halfway through a packaging run. It is the role of the manufacturer of the tablets to recognize quality defects and deal with or replace them. Quality Control must not solely be relied on to identify and address quality issues. Quality should be integrated within the system and preexisting culture. Current Good Manufacturing Practices (cGMP) objectives within the pharmaceutical industry has imposed many constraints over other industries to ensure quality, but quality is still a fundamental CTS consideration. Quality Assurance (QA) undoubtedly has an important role to help develop and define the Quality system, it is nevertheless management's responsibility to create it, and everyone's responsibility to implement it. QA may provide a frame of reference to define "minimum acceptable Quality standards" and perhaps "the gold standard."

Quality should also be assessed in comparison to customer expectations. Phase I dosage forms can be simple, for example. Short shelf life, refrigerated storage, and products requiring significant manipulation before use may be entirely unacceptable for a multicenter phase III study, but absolutely adequate for phase I dosing to achieve expediency.

Planning is an important part of the CTS system and perhaps can be subdivided into immediate, tactical, and strategic. CTS operations frequently plan in depth, but it is important to balance flexibility within such planning processes. Long-term strategic plans can be based on equipment trains/facility issues and capability, volume prediction, growth in budget or resources, preferred vendor or contractor relationships, plus perhaps comparitor agent and drug substance sourcing, for example. Tactical planning may be based on workload prioritization, contract arrangements, and inventory management, whereas immediate planning is more related to completing the job(s) at hand. It is generally a good idea for management to establish a frame of reference to define how, when, and by whom changes can be authorized and this "change control" should be complementary to the CTS planning process.

A good CTS system starts with leadership. It is also important to recognize people attributes and leadership ability for each process within the system. Authority should be delegated, but with delegation, abdication of responsibility should not occur. Instead, it should transform into periodic review. Nevertheless, a CTS system can be completely undermined when a leader attempts to micromanage, for example, by changing a study ship date merely by "managerial pressure" (or fear). A better method is to review the process and the system and ask questions: How can we consistently do it quicker/better (our best always), and how can we get it right all the time, every time?

Leaders should also provide constancy of purpose, or in other words, a strategic vision or plan: Why are we here, and what are we trying to do? Long-term aims and vision are also vitally important to communicate, particularly when system review and improvement are necessary. Moreover, particularly when system overhaul is necessary, good leaders (starting at the top) find ways to strengthen and endure difficult and disconcerting times. Finally, as previously mentioned, CTS leaders should endeavor to create a culture of "individuals win if the CTS system wins." As a mere individual in the system, the CTS "leader" should also therefore accept that pleasing line-management is less critical than delighting the customer (but both are important!).

Education is an important consideration in any CTS system. All should know the system and their role/contribution to making it work. Education (*why*) is complementary too, but distinct from training (*how*). The latter is more tactical, that is, ensuring the skill set is in place to perform the role in the system. Training/education within processes of the CTS system is vitally important. Ensuring that all CRAs understand why and how to order study medication

and comprehend aspects of lead time is a simple example of instantly recognizable, added-value education and training. An important rule is to recognize that if a problem occurs, the process (and/or the understanding of the process) within the system is invariably at fault, not necessarily the individual(s).

Flowcharts may be a useful means to describe and document processes within the system. These may be based on activity deployment, work or information flow, and/or rate/quality limiting aspects. They serve as an excellent basis not only for education and training, but also for managerial review. Flowcharts enable discussion of activities, problems, solutions, and status in terms of a process. Management should carefully review interdependencies. These are not always obvious because actions and consequences may not be simultaneous. An example could be the vendor phase out of a component, which may mean CTS formulation reevaluation (with its consequences), stability testing, and replacement or revision of clinical product inventory. It is better for the system to anticipate such issues rather than react to them. Management, therefore, own any process within the CTS system. Managers must not only maintain the system, but improve it.

IV. CONTINUOUS CTS SYSTEM IMPROVEMENT

A culture of continuous CTS system review and improvement should be encouraged without creating a climate of demoralization. Individuals should be given a "nothing is ever good enough, how can the system be made better?" challenge. It is nevertheless important to convey this message correctly to ensure demoralization does not occur when faced with a "management is never happy" misperception. The added value of processes should be continually examined and opportunities for upgrading explored. Elimination of historical and unnecessary steps (perhaps invisible from outside the CTS system) can be a major way of expediting supply, eliminating bottlenecks, and optimizing resource efficiency. Moreover, an evaluation and redesign of the weakest link or step in the system may actually elicit a profound improvement in the deliverables' quality and timeliness. As a note of caution, the added value of process change is a critical assessment before implementation. It is inappropriate to change "for the sake of It," or worse perhaps in a politically motivated environment "be seen to fix" an overdramatized "system fault." Process change should ideally be founded as a "building process," learning built on continued analysis and improvement measures, rather than a visible, periodic reengineering (or chosen pseudonym, at the time of the event).

A model, derived from an excellent publication (12), is presented in Fig. 1. This suggests a general mechanism for TQM System review, improvement, and implementation. This model is not intended as a definitive action plan, but may clarify the chronological steps within a TQM/CTS Implementation strategy and form the basis of such a plan.

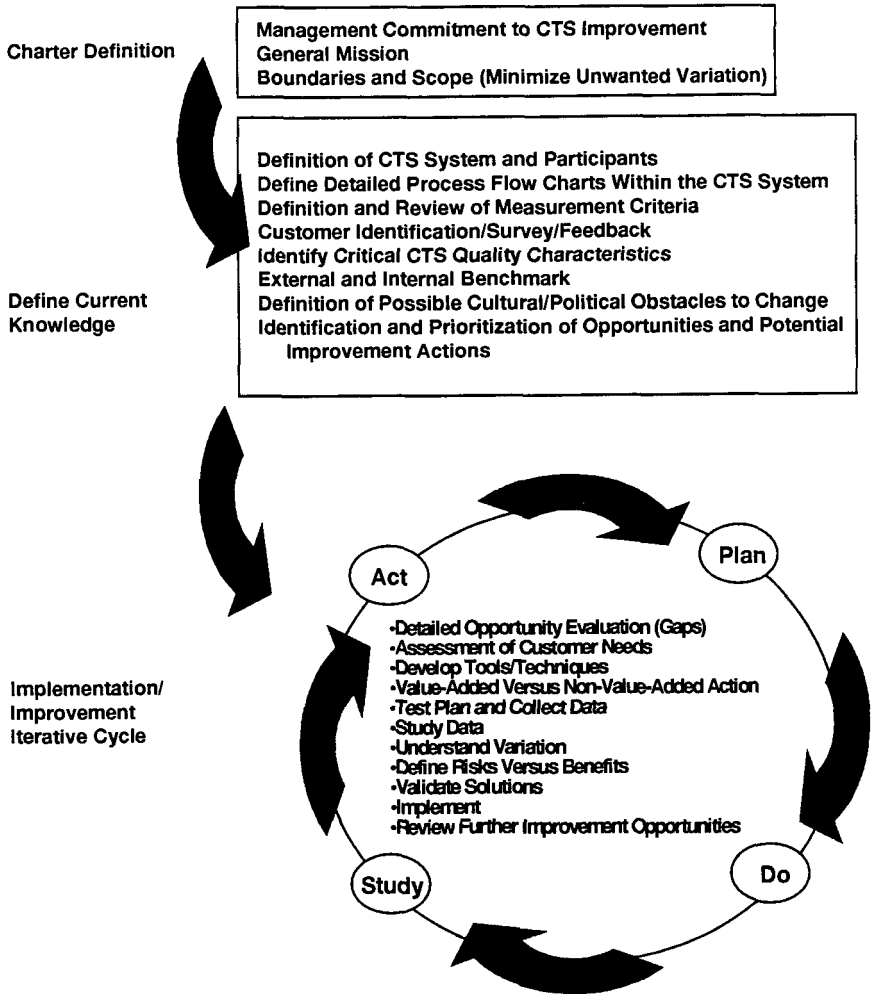

FIG. 1. Clinical trials supplies: A proposed total quality system improvement model.

Technology advances should also be reviewed periodically, and when added-value is determined, validation and subsequent implementation should be considered. Advances in computer systems bring tremendous advantages in terms of randomization with label generation, communication, soft copy files, etc.

Benchmarking is an essential tool for establishing system improvement approaches. However, it is important to note that perceived system upgrades, whether sourced internally or externally, may not be able to be automatically incorporated into the existing system. True understanding, added-value deter-

mination, and adaptation will be required. The Investigation Materials Discussion Group is one of several types of groups that is recommended as a useful CTS benchmarking forum in the United States, and the Association of British Pharmaceutical Industry (Clinical Supplies subsection) is an equivalent U.K. group.

As previously mentioned, a CTS organization that has quality implicit within its strategy must establish a customer focus for the system. Customer research and developing or monitoring of "customer/consumer measures" seeks to evaluate and quantitate system improvements. The use of statistically designed customer questionnaires may be a useful tool. This customer research and planning leads to subtle design and redesign of the system (negative and positive feedback loop) in order to optimize the system and the processes therein. Such activity, however, must be balanced. "Understanding the system," often incorrectly perceived as "stability," is an important prerequisite.

Thus, a critical factor for success in quality improvement is the ability to learn, and it is obviously through learning/understanding that improvements are made. Like customer focus, learning may also be enhanced by fostering teamwork—an element invisible to one team member (perhaps the leader) may be painfully obvious to another. Management may choose to provide training for teams, which will eliminate barriers between departments, managers and workers, and internal and external customers. Moreover, certain individuals may have traits that lend themselves to self and system review and analysis, whereas others may be seen to almost abhor the idea. Such personalities may be used differently in the system. QA should play an important, proactive role in quality and system improvement, not just administration. Aspects such as education, training, and quality objectives are important to introduce proactively, rather than reactively.

Frequently a subtle system change (invisible directly to the customer) can induce profound change in recognizable quality. Trial and error, which may be undertaken to varying degrees of sophistication can be criticized as an approach to system improvement. (However, it is perhaps the biggest single contribution to the evolution of mankind.) Again, critical balance is necessary, review and evaluation of ideas and opportunities before implementation are essential to eliminate "it seemed a good a idea at the time." Suggestions should always be welcomed, but not necessarily implemented directly. They may also spur ideas for review and subsequent implementation (14). Free-spirited personnel may also gain significant satisfaction relating to the implementation of their "good idea." By contrast, many complex models place heavy emphasis on statistical analysis, which when applied can often have a negative impact on individuals fundamentally committed to system improvement. This may sometimes be termed *analysis paralysis*.

Deming's teachings (1,2,4–6) suggest the elimination of numerical goals, where method and quality are more important than the absolute number. Mea-

surement criteria are often taken as a means to merely evaluate CTS productivity. As such, they are a useful tool to justify budget and resources. Additionally, data when plotted on control charts, time, or frequency plots can be used as simple tools for system improvement (12). Decisions on process upgrade, if possible, are best made on data, rather than emotion and perhaps even opinion. Numerical data, therefore, are best used to help or guide, rather than judge. Some examples of CTS measurement criteria are provided in Table 2. Despite its length, this listing is definitely not exhaustive. However, simultaneous tracking of all the parameters cited should not even be remotely considered. Carefully selected measurement criteria should be tracked commensurate with the needs to evaluate processes and the CTS system in terms of productivity, complexity, speed, and efficiency. Thus, chosen process parameters should be *few in number*, *easy to track*, and *absolutely meaningful*. Measurement criteria are an important tool in measuring, monitoring, and evaluating the success of quality improvement actions. "Improvements" that do not really address the underlying causes will be readily detectable. Critically, quality improvement actions should anticipate, if not shape, the future.

The goals for improvement of quality are a common purpose and knowledge of methods, measurements, and concepts, so that change may result in improvement. The aim is continuous improvement in every activity, and an improvement initiative is the responsibility of everyone in the system. Becoming better is logically a more valuable objective than analysis of whether the current "state of the nation" is good or bad. The processes that generate the CTS should be adapted to better its goals. The design of the system and its process should be in constant review and upgrade, matching CTS to customer needs; continuous improvement should thus be a never-ending cycle.

V. VARIATION IN THE CTS SYSTEM

"Life is variation" (1); this is unquestionably true to all those working in the domain of CTS and logistics. There will always be differences between people, service, formulations, protocols, label copy, input/output, regulatory requirements, and time frame. Variation therefore needs to be managed. Variation should be accommodated within an effective process, but can also be used as an indicator of the process, the system, the organization, and even the goal. It is also important to study the common causes of variation(s) in inputs and outputs so that cause and effect mechanisms can be understood and variation may be reduced. There are two types of variation: predictable (it may cause problems, but at least you see it coming and can anticipate the issue) and unpredictable (unforeseen events that impact the process). Murphy's Law is cited as a frequent source of the latter. Measurement and quantification of unpredictable variation are as important as predictable variation. Of course, both sources of variation may have a small or profound impact on outcome and, if coinci-

dent, may actually be synergistic. Undetected variation is perhaps most dangerous—everything is seemingly in control, but reality differs from understanding—and its elimination is a major goal. Variation should be expected as part of the CTS environment, and "ups and downs" are a fact of CTS life. Of importance is the absence of their significant impact on measurable output/results.

Variation can be an important source of information. As with processes, the better the knowledge of variation, the more likely planned changed will result in improvement. Some variation sources can be eliminated. For example, whimsical differences in the overage of study supply medication requested can be ironed out by the ordering process within the system and perhaps by standardization coupled with training/education. Emphasis toward standard clinical protocols, harmonized packaging materials, and stability programs are examples that may also help minimize the complexity that variation may introduce. Thus, the ability of an effective CTS unit to shape the opinion of its customers while still absolutely fulfilling its needs is an important consideration that may help variation management. Variation in output (and its timing) can also be equated to flexibility. For ultimate customer appreciation, as much flexibility as possible should be introduced. It is suggested that core practices, minimum timelines, cGMP standards, and critical procedures be established. Progress should be tracked continually on a highly interactive basis with the customer. This might enable certain negotiable aspects to be incorporated in a CTS time and events schedule, provided none of the core practices are impacted. Thus, if last-minute variations are requested and can be accommodated, they should be, but this must not be a routine occurrence.

Communication and commitment to analyze are important to manage variation in an effective manner to discover what was different, the underlying reason (possibly multiple contributing factors), and the significance or impact on product or process. Variation analysis should be continual not just studied when disaster strikes. The reader is referred to an excellent, contemporary publication (9) that explains strategies for reducing management reactions to variation together with the price of ignorance.

VI. THE BOTTOM LINE

The application of a TQM systems approach to CTS is not "pie-in-the-sky," although at first light it may actually seem so. Moreover, it cannot be a recipe for success, but a practical philosophy continually dependent on sustained, effective implementation. A system heavy of platitudes, but light on substance (15) should of course be avoided. A menu for successful TQM CTS implementation is impossible to define. Nevertheless, it begins with communication and commitment from management and buy-in from all within the CTS system. A general model adapted from literature (12) and applicable to the CTS system

is presented in Fig. 1. As previously stated, the final phase, the improvement cycle is iterative and never ends. In a crisis-like urgent CTS environment, addressing issues on a day-to-day basis, management time to review "not what is being done, but the way in which it is done" is the key factor in building and evolving a professional CTS unit. Time, intellect, and resources must be committed to this crucial ongoing review.

The objective of any professional CTS unit is to become a highly credible, self-learning, proactive operation focusing on speed and quality customer support. This cannot be achieved without an effective CTS system, and the principles of TQM can be applied to understand and evolve this system. So just do it!

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