Clifford L. Nilsen

MANAGING THE ANALYTICAL LABORATORY

PLAIN AND SIMPLE

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First Edition: 1996
ISBN: 1-57491-015-9

Interpharm Press
15 Inverness Way East
Englewood, CO 80112-5776, USA

Phone: 303-662-9101
Fax: 303-754-3953
www.interpharm.com

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Boca Raton London New York Washington, D.C.

Library of Congress Cataloging-in-Publication Data

Catalog record is available from the Library of Congress

Direct all inquiries to CRC Press LLC, 2000 N.W. Corporate Blvd., Boca Raton, Florida 33431.

Interpharm Press is an imprint of CRC Press

No claim to original U.S. Government works
International Standard Book Number 1-57491-015-91
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

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Preface

Managing the Analytical Laboratory: Plain and Simple is just what the title sounds like: a practical manual of laboratory management that focuses on "how to do it," using a common-sense approach that really works. It has evolved during my years of observation, frustrations, and successes as a manager of analytical laboratory operations. Because of the great variety of problems I have encountered—most of which had obvious, simple solutions—I have developed a specialty in "taking the analytical laboratory and making it better."

The approach I use in this book points out the problems associated with the management of analytical laboratories and then offers practical, easy-to-implement solutions. The techniques presented have proven successful in the chemical, food, cosmetic, and pharmaceutical industries in laboratories ranging from quality control to R&D, all with a broad spectrum of personnel, ranging from professionals to hourly workers. In order to illustrate these "how to do it" techniques, I identify problems common to all analytical laboratories first, followed by the special problems of particular types of laboratories.

Chapter 1 gets right to the issue of "What's Really Wrong with My Laboratory," explaining how laboratory problems evolve as a function of corporate culture, pressures of management, and the personalities of scientific professionals. It carefully scrutinizes negative forces—the sources of temptation to do things wrong—in the analytical laboratory.

Subsequent chapters present the step-by-step techniques that can solve particular problems. The "how to do its" are linked to specific problems, establishing clear problem-solution pathways. With these chapters, I provide numerous SOPs, ready for immediate use or easy adaptation. In Chapters 8–10, I describe the SPACE System of Laboratory Management (SPACE), a modus operandi for analytical laboratory management that embraces all of the "how to do it" techniques.

In today's climate of regulation and competition, I believe you will find this book has special value.

ACKNOWLEDGEMENTS

I would like to thank several of my colleagues, especially Dr. Aaron Cooper, Dr. Kenneth Kelly, and my good friends, Norm and Sweeta Alworth, Len Larcara, and Bob McCrimlisk, at MPT. Special thanks to Amy Davis and the Interpharm editorial staff for all their help and encouragement.

Most of all, I would like to thank my beautiful wife Francine for her love, support, and patience.

Clifford L. Nilsen
March 1996

CHAPTER

1

Introduction

In any company operation, including the analytical laboratory, the flow of work and communication must augment the business success of the organization. Poor coordination and communication will inevitably lead to poor performance and failure to achieve goals and meet deadlines. Because of the detailed nature of their work and possible consequences of errors or bad data, laboratory personnel in particular need to follow proper procedures and protocol. Laboratory managers or supervisors, therefore, because they are accountable for the work of their analysts, have the additional responsibility to carry out a management plan that is consistent with the needs of the department and supports overall company objectives. The plan must provide for accuracy of data, timeliness of reporting, and compliance with any and all regulatory agencies.

The analytical laboratory is, by definition, a service group. The service provided is analysis of samples submitted to the laboratory. Whether a laboratory is part of a Quality Control (QC) unit, a research and development (R&D) group, or an analytical consulting organization, the service is expected to provide accurate and timely results on a consistent basis. The data generated by an analytical laboratory might be the basis for a decision to continue to the next step of a plant process, to package a finished product for shipment, to release a raw material for production use, or to take action concerning a competitor's product or customer complaint.

If the data are not accurate or timely, the outcome can be disastrous. Poor data from a quality control unit, for example, can lead to reworking of batches, delays in shipment of goods to customers, inadvertent rejection of good materials, release of out-of-spec batches, lost dollars, lost sales, damage to the laboratory's credibility, and perhaps even a threat to consumer safety. A laboratory that produces shoddy data on a regular basis will quickly gain a new manager or supervisor.

An analytical laboratory may be either a well-run, respected service organization or a nightmare, fraught with problems such as low esteem and lack of respect. Correcting problems that have developed over time is more difficult than is the effort required to operate a laboratory correctly from day one. This book will explore problem-solution relationships for both good and bad laboratories. Since those requiring analytical laboratory services are in effect customers, the primary goal of the laboratory manager should be customer satisfaction.

1.1 THE FLOW OF WORK

In order to manage the analytical laboratory effectively and to provide the quality of data and level of service that is expected by the customer, the manager needs to ask three basic questions.

- How do I get my work?
- What do I do with the work when I get it?
- What do I do with the work when it's done?

Knowing the answers to these three questions is the key to building a strong, structured management plan for a laboratory.

1.1.1 How Do I Get My Work?

The manager must find out what departments submit work to the laboratory, how many people are involved in the delivery of that work (i.e., chain of custody), the time frame for delivery of work, and most important, how the work is logged into the laboratory system so that it can be uniquely identified for processing.

1.1.2 What Do I Do with the Work When I Get It?

A definite plan for handling a sample must be followed after it has been logged into the laboratory system. It must be given a priority and evaluated in terms of what tests are to be done. These tests must be assigned, deadlines or promised times of completion must be communicated to the customer, and the actual testing has to be done.

1.1.3 What Do I Do with the Work When It's Done?

This question involves follow up and communication. The work needs to be documented, audited, and reported to the customer.

1.2 TOOLS OF THE TRADE

How often are laboratory managers plagued by pressure from manufacturing to release samples, mistakes by chemists, equipment breakdowns, out-of-stock chemicals, missing samples, and over commitment because of heavy workloads? Poor managers may blame such problems on the people they work with or just plain bad luck. Good managers, on the other hand, make their own luck by developing a plan that allows for deviations, unplanned events, and fluctuating workflow.

How do people become good managers who can consistently handle the pressures of laboratory life and deliver time after time? How do they maintain a high standard of credibility and employee satisfaction? Mastering the tools of the trade can help.

Fourteen (14) management tools will be applied throughout this work, not only to answer the three basic questions, but also individually and in combination to solve a myriad of laboratory problems. Their application should improve the quality, efficiency, and efficacy of any analytical laboratory operation. The following techniques are discussed in chapters 3–7.

1. Self-contained paperwork systems
2. Task-oriented workload
3. Support systems
4. Work-hour matching
5. Safety/housekeeping awareness
6. Passenger removal
7. Training
8. Total-immersion supervision
9. SWA with intercomm (structured workload assignments with intercommunications)
10. Interlaboratory efficiency matching
11. Accelerated problem-solution loop
12. Computerized tracking
13. Laboratory geography and technology
14. Quality Assurance for the laboratory

1.3 WHAT'S REALLY WRONG WITH MY LABORATORY?

The first step in developing a sound, structured management plan for the laboratory is to clearly identify problems. Problems in the laboratory are derived from a wide variety of sources, often making identification difficult. Some common sources are people, environment, training, attitude and style of management, workload/pressure, communications, and degree of professionalism. More often than not, problems arise as a result of a combination of factors that can be collectively referred to as corporate culture.

In order to deal effectively with the topic of analytical laboratory management, one must look not only at the supervisory part of the operation, but also at some technical aspects, since there is always an intimate interaction between the two. Supervisory style and corporate culture can have a direct effect on how a scientific professional or technician performs technical tasks that range from receipt of sample to the final report. Quality of work, productivity, attentiveness to safety, and conformance to standard operating procedures are all directly influenced by the style and method of management.

The faults of a laboratory are usually a combination of sloppy practices and pressure from management to meet goals, such as production or shipping deadlines. Most workers strive for conformance to scientific procedures while producing quality work. Given enough time, a scientist can analyze a sample, run the appropriate standards and controls, scrutinize the data, and produce reliable results. However, once deadlines come into play, particularly those tied to dollar factors such as shipping dates and standard operating costs, and once output becomes the driving force, quality of

work is liable to suffer. Worst-case scenarios are usually seen in high volume operations, such as QC and process control laboratories.

1.3.1 The Downward Spiral

As time goes on, a trade-off of quality for output tends to develop. It isn't until outside observation comes into play, such as an FDA inspection or a quality audit by a key account, that the accumulated deficiencies appear and corrective action is undertaken. At this point, the cost of getting back on track can be significant, particularly in regulated environments such as the pharmaceutical industry.

1.3.2 Sorting It All Out

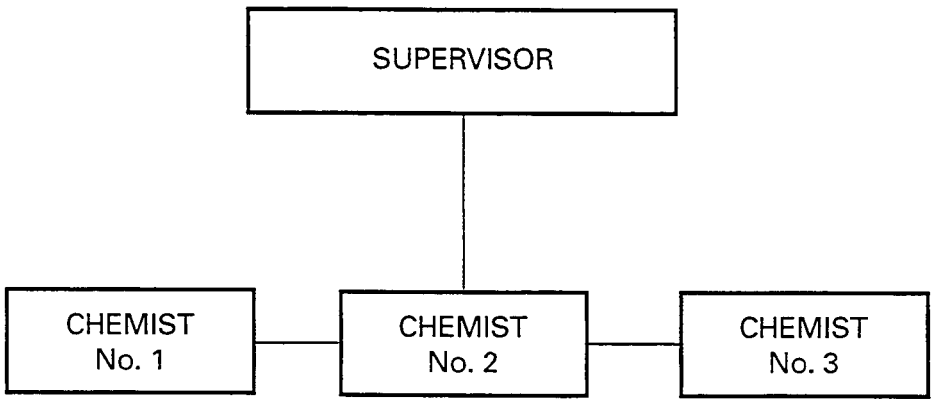
Unfortunately, many laboratories fall victim to this downward spiral. Many have evolved into worst cases that are in desperate need of assistance. Of course, preventing the downward spiral before it occurs is best. Techniques for doing this are presented in later chapters. However, when problems already exist, immediate solutions are required, followed by measures to prevent their recurrence.

In order to understand both cure and prevention, it is first necessary to identify and examine two negative forces present to some degree in nearly every analytical laboratory. These forces tend to creep subtly and gradually into the laboratory, going unnoticed until the damage has been done. Labelled the "Storytelling Syndrome" and the "Teacher's Pet Syndrome" respectively, each is generally the outgrowth of corporate culture and can be resisted and controlled by only the most disciplined of managers.

1.3.3 The Storytelling Syndrome

Newlabs, Inc. was preparing to begin manufacture of pharmaceuticals on January 1. The company hired all laboratory personnel three months in advance so that they would be properly trained and fully familiar with all standard operating procedures (SOPs). The initial staffing consisted of a supervisor and three chemists (see Figure 1.1).

Figure 1.1. Laboratory organization chart (Time: Zero).



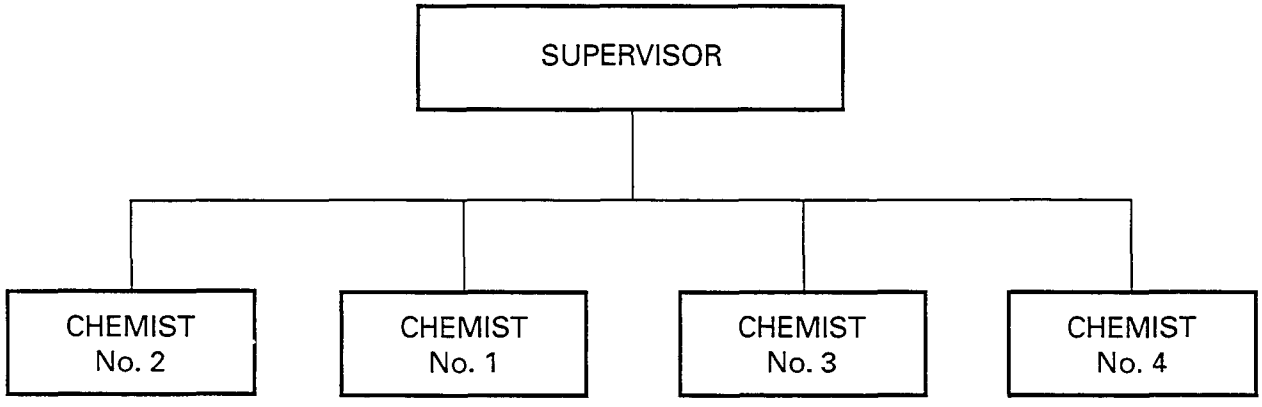
The supervisor was trained by her manager, after which she personally trained the three chemists. Each chemist was consistently trained, studying all written procedures and using practice samples to learn laboratory operations. The chemists were allowed to take their time and do it right the first time. Without manufacturing pressures to worry about, the supervisor could devote sufficient time and energy to thorough training.

After one year of operation, the company was doing well and had grown busy enough to add an additional chemist to the staff (see Figure 1.2).

After a year of manufacturing, the supervisor assumed that the initial training she gave the first three chemists was sufficient. Her time was now consumed by everyday deadlines and schedules, so follow-up training had been minimal. Each of the original chemists had also been subjected to workload pressures. As time went by, the chemists became familiar with methods and procedures and started doing many tests from memory, instead of referring to written procedures each and every time. Because of this, slight deviations crept into their work: the first part of the downward spiral had begun.

Meanwhile, the new chemist needed training, but the supervisor was too busy to devote full time to this task. She provided some initial training, but then informed the new chemist that she would not always be available and suggested that he ask one of the original three chemists for help with problems or questions. The new chemist, wanting to succeed, took his supervisor seriously and ended up being trained by the original chemists. His training, as a result, was adulterated compared to that given the original three chemists. The new analyst read all the SOPs and was given orientation, but with the plant running and productivity a driving force, he was expected to go on-line as quickly as possible. There were samples to be run and no time to read the written procedures thoroughly with each analysis. The new chemist, when rushed, relied on shortcuts taught to him by his colleagues rather than following the written procedure, thinking it must be right since the others did it that way. The process of poor practices was off and running.

Figure 1.2. Lab department organization chart (Time: 1 Year).



After two years in business, sales had doubled. The company hired a second lab supervisor and two more chemists, presenting a whole new set of problems. The new supervisor and chemists were hired for a recently created evening shift. Not only would training have to be provided, but communications would need to be established between the shifts to allow for a contiguous flow of work and consistent operating procedures.

A sensible way to bring new people into an existing organization that is already producing is a major problem in today's industrial environment. In the case of Newlabs, Inc., who would train the new supervisor and the two new chemists, and how would the quality of performance be affected by increased workload? The laboratory organization chart is shown on Figure 1.3.

Supervisor 2 was supposed to be trained by the manager to whom both supervisors reported. The manager was too busy and delegated training of supervisor 2 to supervisor 1. Since supervisor 1 had two years to form her own habits, the training of supervisor 2 was adulterated compared to the training received by supervisor 1. Instead of going over each step of each written procedure, supervisor 1 merely told the new supervisor to read the procedures. Day-to-day activities had become so overwhelming that time for methodical, step-by-step training was minimal.

The new supervisor and his chemists were trained during the day shift for a short period before working evenings. Their training was carried out by both supervisor 1 and the four chemists on the day shift, all of whom were doing things somewhat differently from one another. The result was a system of procedures and methods that was disassociated rather than standardized. No one had time for training, very little reference was made to written procedures in day-to-day work, workload became heavier, and the number emergencies was escalating.

As the company continued to grow, more chemists and supervisors were hired. Each one was trained and did work in a way slightly different from that of his or her predecessor, adding his or her own style to the work. Like a story or joke that is repeated from person to person, changing every time it is told, each SOP or written laboratory procedure was altered as it was passed on.

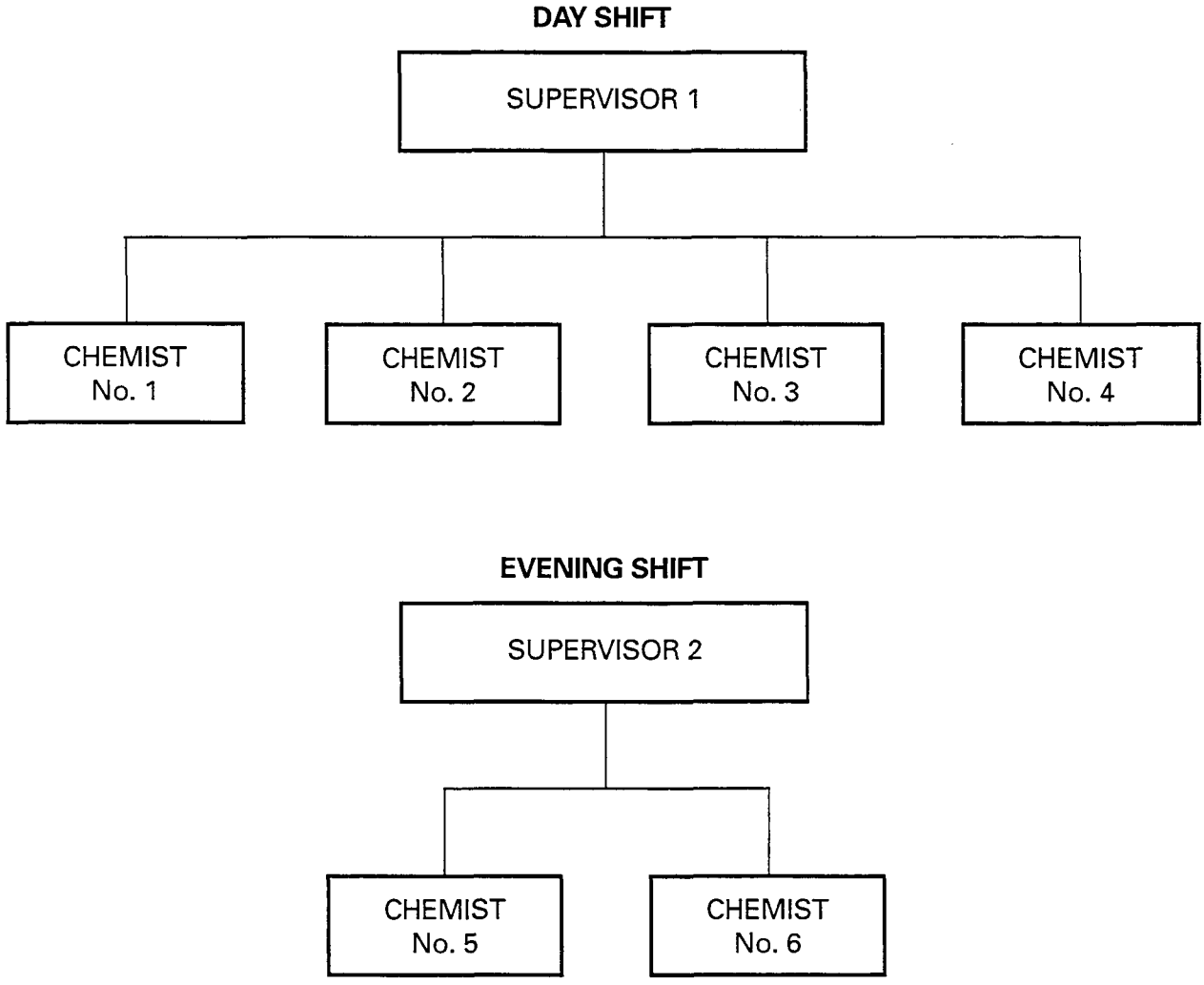
The Storytelling Syndrome is clearly a case of commitment to training yielding to workload pressures. No one will ever say that they are against training, but scheduling employees for training sessions during working hours often leads managers and supervisors to claim that they are too busy to spare the people. Managers and supervisors often fail to realize that investment in training, although it means a very short-term productivity loss, will be offset many times over by the permanent gains that result from the quality performance of well-trained laboratory personnel.

The Storytelling Syndrome can be avoided by establishing a laboratory management program that includes a firm commitment to training and high-quality performance. In later chapters, specific techniques for executing and maintaining a solid technical training program are presented in a how-to-do-it format.

1.3.4 The Teacher's Pet Syndrome

Almost everyone wants to be appreciated, recognized, and well thought of by associates and coworkers, but more than that, employees want to please their bosses. Just as most of us, as children,

Figure 1.3. Lab department organization chart (Time: 2 Years).



tried to win teacher's favor (teacher's pet), we strive to please our managers and supervisors in the workplace. After all, a job should provide the means to achieve personal and professional goals that yield both financial and emotional rewards.

With this in mind, people try to do their best on the job. Unfortunately, many laboratory analysts carry the desire to succeed to extremes. This extreme desire to please may be the result of job insecurity (poor job market or an employee returns to work after extended unemployment), fear of punishment (when a supervisor is unfair, abusive, or intimidating), or simply an attempt to succeed at an assigned task.

Here is a typical series of events.

> A chemist is assigned to carry out an analysis which, if properly performed at a normal rate of speed, will take two (2) hours.
>
> The supervisor says, "I need it sooner than two hours from now" and pressures the chemist to speed things up.
>
> The chemist, to please the supervisor and to keep from looking bad, completes the task in one and one-half hours, but makes a mistake because she rushed. Now the analysis must be repeated.

Two more chemists repeat the task, each taking two hours to do it right. The supervisor has to fill out an investigation report to explain the bad data generated by the chemist who rushed. The report takes one hour to complete.

A two-hour task has taken six and one-half hours because the chemist, in order to please the boss, rushed the job instead of insisting that, to do the job right the first time, she would need two hours. Such a stand might have enlightened the supervisor, encouraging him to step back and think a moment. Perhaps then, the supervisor would have responded in reasonable fashion, giving the chemist help if the analysis was needed in less than two hours.

However, such an outcome assumes a reasonable supervisor and an astute, confident analyst. Supervisors are often inordinately busy, usually juggling too many balls at once. It is the responsibility of the analyst to alert the supervisor to potential problems. Employees should be encouraged to take such action, providing reasonable feedback. A good supervisor will appreciate this and grow to depend on that analyst's judgment. On the other hand, if the supervisor and analyst do not or cannot communicate, then the supervisor's instructions will be followed blindly without regard to consequences. The result will be inefficiency, poor quality, and low morale.

In this particular example, all that was lost was time. But suppose the supervisor had been reprimanded by his manager for taking too much time. When a future job has to be pushed, the supervisor will again pressure the chemist to rush. This time, despite her objections, she may be forced to do so. Now the classic situation has developed where the chemist, in order to get the job done in one and one-half hours, may have to deviate from normal procedure. The chemist will do everything possible to produce good results in one and one-half hours, yes, even if he or she has to cheat. The more often people are pressured to rush and take shortcuts, the greater the probability that they will deviate from standard procedures, and they may be tempted to engage in unethical or dishonest scientific practices.

1.4 SOME OTHER CONCERNS

While the Storytelling and Teacher's Pet Syndromes are the most serious long-term problems that afflict the analytical laboratory, there are also a variety of immediate emergencies and problems that burden it on a daily basis. Most are easily identified and may be human or technical in nature.

1.4.1 Perception Is Everything

In workplace environments where communications are poor or inconsistent among different levels of an organization, whether something is true or false is, for all practical purposes, irrelevant. What people perceive is what they believe. The simple truism that "one's perception is one's truth" has probably caused more problems than any other factor in the workplace, and the analytical laboratory is no exception. With this in mind, this book will present two aspects of the modern analytical laboratory from several functional angles in order to pinpoint areas of concern.

1.4.2 The Multinational Work Force

Today's analytical laboratory is staffed with individuals of many nationalities, representing a wide variety of cultures and customs. The multiethnic workplace is here to stay and can be a rich and rewarding environment, but it is also a breeding ground for misperceptions. The quality of management can make all the difference in preventing misunderstandings. Managers and supervisors need to learn as much as possible about the cultures and customs of their staffs in order to improve communications and avoid misperceptions. A manager who schedules a department luncheon on a staff member's religious holiday for example, might be perceived as ignorant at best, or at worst, deliberately discriminatory.

1.4.3 Level of Skill

Ninety-five percent of all problems in analytical chemistry are related to technique. The personal technique or skill that is the mark of a true analyst is a combination of wide practical knowledge, strong common sense, and good eye-hand coordination.

Many young chemists entering industry today seem to lack the skill of their predecessors. They appear poorly prepared compared to the chemists of 20 or 30 years ago. As technology advances, the situation seems to deteriorate. Why?

It is felt that the explanation lies in the evolution of technology, coupled with a changing chemistry curriculum in colleges and universities and the teaching of chemistry, particularly in the area of laboratory skills.

Today's laboratories boast the most modern instrumentation. A typical analytical laboratory will have at least one each of the following:

- High pressure liquid chromatograph
- Gas chromatograph
- Fourier-transform IR spectrophotometer
- Atomic absorption spectrometer
- Mass spectrometer
- NMR (nuclear magnetic resonance spectrometer)
- Capillary electrophoresis
- Robotics

In addition, most laboratories will also have such items as fraction collectors, electronic balances, automatic dilution and aliquoting devices, and a wide variety of spectrophotometers, not to mention computers and sophisticated data systems. The typical analytical laboratory of 1970, on the other hand, would have had UV and IR spectrophotometers, a simple gas chromatograph, several analytical balances, and a great deal of glassware.

Today's laboratory with its technology and sophistication is certainly safer and more efficient, but because of the automation, its operations require less understanding of the chemistry. Today's analyst tends to know what to do without always understanding why. In older analytical laboratories, sample preparation and handling, including weighing, extractions, and final dilutions, accounted for about 80–90 percent of the analytical procedure, with the actual analytical finish and calculations being only a small part of the analysis. By contrast, today's analytical methods center primarily on instrument conditions, and calibration, with sample preparation playing a minimal role. Today's analyst finds that the laboratory's analytical scheme is often "dilute it and shoot it": prepare a sample, put it into the instrument autosampler, push a button, and wait for the result. Less technique is required, because there is less need for physical handling of a sample prior to the analytical finish, or for final measurement prior to calculation.

In 1970, for example, a cough syrup containing two ingredients would have been weighed and brought to some known volume. Then, a portion would have been accurately transferred to a separatory funnel, an ion exchange column, or perhaps a chromatography column. After this, a separation of the two components would have been made through manual extraction based on a chemical principal such as solubility, acid-base character, difference in pK values, functional group characteristics, or ion-pairing. The extracts of each component would have then been cleaned up, diluted to some known volume, and measured for concentration of the analyte. The measurement might have been direct or perhaps preceded by a chemical derivitization. All of this physical handling would have been accomplished quantitatively without losses—a task requiring excellent technique. In addition, the steps required to go from sample weighing to final result served to reinforce an understanding of the chemistry. By contrast, today's analyst merely weighs a sample, and in the worst case, shakes, filters, and dilutes it. After that, the instruments do the rest.

This emphasis on the instruments, rather than chemistry, is seen in the abundance of SOPs and written procedures that describe instrument attributes, such as calibration, system suitability, resolution, and tailing factors. With the introduction of the microprocessor in the late 1970s and its impact on technology, it was thought that chemists would need a good working knowledge of electronics and computers to be successful in the modern analytical laboratory. This turned out to be correct, although the price was a loss of training in chemistry.

Because the sophistication and automation of today's instruments tend to minimize the need for subjective measurement and observation, an unskilled person can be trained within six weeks to be an effective, accurate, and productive analyst. This person may know little chemistry, but can work productively as an "analytical chemist," performing analyses and turning in correct results *as long as nothing goes wrong*. When something does go wrong, analysts who do not really understand chemistry cannot recognize problems effectively. Even when things go right, whether in methods development or routine analysis, an analyst with an understanding of the chemistry will produce better quality data, work more effectively, and be able to improve his or her science.

Unfortunately, chemistry curricula of today do not seem to provide the rigorous training experienced by students in the past. Courses in analytical chemistry that include separate semesters for qualitative analysis, volumetric analysis, and gravimetric analysis are rare. Analysts in contemporary laboratories may not have been trained to carry a crucible, dilute a flask to the mark, transfer samples quantitatively, or do a calculation involving simple concepts such as milliequivalents. Too much emphasis has been placed on computers and not enough on analytical chemistry as a distinct and important discipline.

This means that managers and supervisors must focus heavily on education in the workplace. Since industry supervisors cannot control college curricula or previous training, they must identify deficiencies in the fundamental skills of analysts and make every effort to correct those deficiencies. It may be difficult to evaluate level of skill based on education. In subsequent chapters, identifying and dealing with the problem of poor analytical skills will be discussed in detail.

CHAPTER

2

Standard Operating Procedures

2.1 INTRODUCTION

The analytical laboratory lives and dies by its standard operating procedures (SOPs). A principal focus of laboratory inspection by the U.S. Food and Drug Administration (FDA) is that adequate SOPs exist and that a firm's SOPs are being followed as written. Therefore, properly written SOPs are a critical component of the analytical laboratory. Poorly written SOPs, or SOPs that are not being followed, are a major source of inspectional observations by FDA.

2.2 THE GOLDEN RULES OF SOPs

Well written SOPs are easily developed using the following rules:

- An SOP should be detailed enough to adequately define the task it purports to describe.
- An SOP should be general enough not to box the user into a situation where efficiency is lost or management prerogative is constrained.

For example, if one were to write an SOP describing the calibration of an analytical instrument that is used almost every day, and the SOP required a daily calibration frequency, then that instrument would have to be calibrated daily, whether it was used that day or not. Alternately, the SOP might have specified the calibration frequency as daily or when in use. Under the latter, the instrument would only be calibrated on days it was used, maximizing efficiency.

Another example is where management prerogative or scientific judgement is limited by language used in an SOP: a procedure calls for 200 mg of sample to be weighed into a 100.0 ml volumetric flask, dissolved in water, and diluted to volume. If only 150 mg of sample were available, would weighing less than 200 mg, 100 mg to 50.0 ml for instance, constitute a breach of the SOP? Probably not, since this situation comes under reasonable scientific judgement, but a hard-nosed FDA investigator might think so, claiming that the firm should have collected enough of a sample to

Don't be trapped in a box by SOPs

follow the SOP as written. It would be more flexible to write a procedure that says to weigh about 200 mg of sample into a 100 ml volumetric flask to produce a solution containing 2 mg/ml of sample, thereby clarifying the option to use reasonable scientific judgement should an equivalent sample or solution need to be prepared.

2.3 ANATOMY

When writing SOPs, the basic structure (anatomy) should be as follows:

1. Purpose
2. Scope
3. Responsibility
4. Frequency
5. Procedure
6. History or Change Control Attachment

2.3.1 Purpose

This section simply states the objective of the SOP, for example, "To define a procedure for calibration of analytical balances."

2.3.2 Scope

This section defines the applicability of the SOP. The calibration of analytical balances might have a scope of "QC labs and R&D labs in facility number one," for example.

2.3.3 Responsibility

This refers to who is responsible for implementation of the SOP. This could be a department such as QA or an individual such as the QA supervisor or a QC chemist.

2.3.4 Frequency

This section defines the interval at which the SOP will be applied, such as daily, weekly, monthly, or yearly.

2.3.5 Procedure

This is the actual detailed "how to do it" part of the SOP, and should be written in accordance with the criteria suggested in section 2.2.

2.3.6 History or Change Control

This is an extremely important part that defines the reason for issuing an SOP, and if it is a revision, why the revision was issued and approved. This makes for an iron-clad audit trail when reviewing reasons for changes.

2.4 APPROVALS

In addition to the sections mentioned under 2.3, all SOPs should include the name of the author or authors and the signatures of reviewers and approvers on the first page of the SOP, along with title, date, number of pages, and revision number. Each subsequent page should contain the title, page number, and revision number.

2.5 HOW LONG SHOULD AN SOP BE?

There are many styles of SOP development. Some writers prefer extremely detailed ones that leave nothing to chance, while others prefer short SOPs that define the task in less detail but are easier to read and to follow. This author prefers the shorter SOP, since they make for a more smoothly run laboratory, particularly in the pharmaceutical industry. A typical firm might have hundreds or even thousands of SOPs—100 or more just for the laboratory and its related functions. Shorter SOPs make training easier and allow for dynamic use of those SOPs, since they do not overly confine the user.

2.6 WHAT ABOUT STYLE?

There are two basic ways to format an SOP: free-form and military style. The free-form style uses headings under which paragraphs are written. The military style uses a numbering system for sections and paragraphs. This author prefers the military style, because any particular section is easy to reference. Examples of both are presented at the end of this chapter.

2.7 SAMPLE SOPs

At the end of several chapters in this book, there are generic SOPs covering topics discussed in those chapters. These SOPs add to and expand upon the "how to do it" tools presented herein. The reader is free to use these as basic SOPs or as a supplement to their existing SOP library. The style is military and short, except for such SOPs as analytical methods and validation protocols where extreme detail is needed by definition.

The company name Newlabs, Inc., used in chapter 1, will be the name used on all sample SOPs.

2.8 A FINAL NOTE

Regardless of style, length, or language, it is important to note that any SOP, once written and approved, must be followed as written. It is much more difficult to change an approved SOP than it is to write it correctly the first time. The FDA is not interested in style and length; rather, they are concerned as to whether or not SOPs exist for each operation performed by the laboratory, and whether or not they are being followed as written. Remember, it's *your SOP*; write it the way you want, but once written and approved, *it must be followed without deviation.*

STANDARD OPERATING PROCEDURES

CHAPTER 2: STANDARD OPERATING PROCEDURES

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **How to Write a Laboratory Standard Operating Procedure**	NUMBER: **001**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define the procedure and format for a Laboratory Standard Operating Procedure.

1.2 To define the military numbering system for Laboratory Standard Operating Procedures.

2.0 SCOPE:

2.1 Analytical laboratories, Quality Control, R&D, and Quality Assurance.

3.0 RESPONSIBILITY:

3.1 Laboratory directors, managers, supervisors, and technical writers.

4.0 FREQUENCY:

4.1 When generating a new laboratory SOP.

4.2 When revising an existing laboratory SOP.

5.0 PROCEDURE:

5.1 Set up the SOP document to have the following sections:

5.1.1 Purpose

5.1.2 Scope

5.1.3 Responsibility

5.1.4 Frequency

5.1.5 Procedure

5.1.6 History

5.2 Description of Parts

5.2.1 "Purpose simply states the objective of the SOP, for example, "To define a procedure for calibration of analytical balances."

5.2.2 "Scope" defines the applicability of the SOP. The calibration of analytical balances might have a scope of "QC labs and R&D labs in facility number one," for example.

5.2.3 "Responsibility" refers to who is responsible for implementation of the SOP. This could a department such as QA or an individual such as the QA supervisor of QC chemists.

5.2.4 "Frequency" defines the interval at which the SOP will be applied, such as daily, weekly, monthly, or yearly.

5.2.5 "Procedure" is the actual detailed "how to do it" part of the SOP. It should be detailed enough to be followed as intended, but not so detailed that it restricts reasonable scientific judgement from being exercised.

5.2.6 "History or change control" defines the age of an SOP, and if it is a revision, why the revision was issued and approved. This makes for an iron-clad audit trail when reviewing reasons for changes.

5.3 Military Numbering

5.3.1 Sections are to be numbered using the military system (e.g., 1.0, 1.1, 1.1.1). Do not use more than four levels if possible (e.g., 1.1.1.1). If additional levels are required, use bullet points, dashes, or other means of highlighting.

5.4 Approvals

5.4.1 All SOPs should have the name of the author or authors, and the signatures of reviewers and approvers on the first page of the SOP, along with title, date, number of pages, and revision number. Each subsequent page should contain the title, page number, and revision number.

6.0 HISTORY:

6.1 REVISION - 0; Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **How to Write a Laboratory Standard Operating Procedure**	NUMBER: **002**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

PURPOSE:

To define the procedure and format for a Laboratory Standard Operating Procedure.

SCOPE:

Analytical laboratories, Quality Control, R&D, and Quality Assurance.

RESPONSIBILITY:

Laboratory directors, managers, supervisors, and technical writers.

FREQUENCY:

When generating a new laboratory SOP.

When revising an existing laboratory SOP.

PROCEDURE:

Set up the SOP document to have the following sections:

Purpose

Scope

Responsibility

Frequency

Procedure

History

Description of Parts

"Purpose" simply states the purpose of the SOP, for example, "To define a procedure for calibration of analytical balances."

"Scope" defines the applicability of the SOP. The calibration of analytical balances might have a scope of "QC labs and R&D labs in facility number one," for example.

"Responsibility" refers to who is responsible for implementation of the SOP. This could a department such as QA or an individual such as the QA supervisor of QC chemists.

"Frequency" defines the interval at which the SOP will be applied, such as daily, weekly, monthly, or yearly.

"Procedure" is the actual detailed "how to do it" part of the SOP. It should be detailed enough to be followed as intended, but not so detailed that it restricts reasonable scientific judgement from being exercised.

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HISTORY:

REVISION - 0; Supersedes - Original
Reason - N/A

CHAPTER

3

Tools of the Trade: Efficiency and Safety

The 14 tools of the trade, or laboratory management techniques, listed at the end of chapter 1 are now presented in detail. Each tool will be applied in a total management plan as part of the SPACE (safety, productivity, accuracy, credibility, education) system of laboratory management.

3.1 SELF-CONTAINED PAPERWORK SYSTEM

One of the hottest terms in today's workplace is *paperwork reduction.* This concept is being applied in both private industry and government. In the analytical laboratory environment, it offers the benefit of better accuracy, fewer errors, increased productivity, and more consistent compliance with good laboratory practices. The self-contained paperwork system is a form of paperwork reduction that is designed to facilitate the efficiency and productivity of the analytical laboratory, and minimizes the traditional use of hardbound notebooks.

3.1.1 Notebooks

A typical Quality Control laboratory, for example, would receive samples; log those samples into the laboratory system; set up a notebook page to accommodate the analytical data that will be generated; do the actual analyses; record the raw data, calculations, and results; and fill out a final analytical report.

Look at the paperwork: The analyst carries around a notebook in which raw data, such as sample weights and titration data, are recorded as they are generated. This notebook is physically carried from place to place as the analyst moves around the laboratory in the course of processing samples. After the work is done, it must be transcribed from the notebook onto a finished report form, such as a finished product release sheet. The auditor or supervisor has to check the notebook and the release sheet to look for transcription errors, to check calculations, and to be sure that all specifications are met prior to final approval.

3.1.2 Worksheets

An alternative is use of laboratory worksheets. Laboratory worksheets are preprinted forms that contain information, such as product name, batch number, lot number, sampling information (number of drums or containers), blank spaces for raw data (such as sample weights), plus preprinted calculations with blank spaces left for actual data, and blank lines for results and signatures. Worksheets can serve as a combination notebook and report form that can be filed with batch records or manufacturing reports to make up a self-contained paperwork package for that particular batch of material.

Using the worksheet approach, notebooks are eliminated (notebookless lab), transcription errors and auditing time are dramatically reduced, traceability of data is more efficient, and inspection by regulatory agencies is better managed, because inspection of a batch record will only show lab data for that batch. Opportunities for *notebook browsing* (inspecting notebook pages without looking for a specific item) are eliminated.

Figures 3.1 and 3.2 show two types of laboratory worksheets. The worksheet sample depicted in Figure 3.1 can be used as a raw material, process intermediate, or finished product worksheet. Analytical results are entered directly on the worksheet. For tests requiring raw data, such as sample weights, titration values, or any other empirical measurement, blanks are provided. This approach uses preprinted calculations. Data, such as dilution factors and equivalent weights, are also preprinted. This approach minimizes the subjectivity of data transcription and makes the auditing or checking function much simpler and more reliable. Data from instruments such as spectra, chromatograms, and titration curves are attached to the worksheet, making up a complete analytical package for any subject sample. Results and raw data are in one place and can be filed as such for further reference. The worksheets can be carried around the laboratory on a clipboard along with other worksheets.

The worksheet shown in Figure 3.1 is particularly versatile, because it can be used in several ways. For finished products or raw materials, the form is used as is, but for process intermediates, the top half can be torn off and sent to Manufacturing as a report of results, while the lower half is retained for filing.

The worksheet shown by Figure 3.2 is a different approach, because it is not a true worksheet, but rather a finished result report sheet. This type of document is useful in that it gives a very detailed description of the material under test. Included are such items as company ID, material name, manufacturing date, and quantity. The strongest feature of this type of worksheet is that test names along with their respective specification limits are shown on a single page. Results are entered next to the specifications, along with the analyst's initials, references, and date. In addition, provision is made to record both auditing of results and final material disposition. This type of worksheet is excellent for regulated industries such as pharmaceuticals and foods, where adherence to specifications and proper auditing and checking are enforced though regulatory inspections.

While both of the worksheets are well suited for their respective tasks, neither is perfect. A better approach is a combination of the two. Figure 3.2 is well suited as a result sheet, while Figure 3.1

Figure 3.1. Example of a worksheet.

200C

Batch _____ Date _____

Lot _____ Analyst _____

(1) %Ethanol (2) %Acidity (3) Sp.G.

_____ _____ _____

200C

Batch _____ Date _____

Lot _____ Analyst _____

(1)%Ethanol (Attach GC readout—Report %ETOH) _____

---

(2) %Acidity (50 ml sample, 0.1N NaOH - Run a blank)

$$\frac{(\text{Sample } \_\_\_\_ - \text{Blk } \_\_\_\_) \times N \_\_\_\_ \times 0.060}{50} \times 100 = \_\_\_\_\%$$

---

(3) Sp.G @ 25/25 _____

Analyst _____

Figure 3.2. Example of a finished result report sheet.

COMPANY NAME
ADDRESS

RAW MATERIAL SPECIFICATION AND ANALYTICAL REPORT SHEET

RETEST DATE _____

Material _____

Code _____ Control No. _____

Manuf. Date _____ Lot No. _____

Quantity _____ Received _____

SAMPLING DATA: Sample Size _____

No. of Containers Sampled _____ Sampled by _____

TEST	METHOD	SPECS	RESULT	ANALYST	REF.	DATE

REMARKS: * RETEST ON A YEARLY BASIS

MANUFACTURER'S C of A ALSO REQUIRED FOR RELEASE

Audited by _____ Date _____

Disposition _____ By _____ Date _____

can be used for entering raw data and calculations. Raw data, such as chromatograms, attached to the combination worksheets will serve as a complete analytical record for any material under test. It is suggested that these analytical records be filed together with the batch record for the product being tested.

In the event of a regulatory inspection, batch records will contain the analytical data for that batch only. The worksheet approach eliminates unnecessary *fishing expeditions* by FDA inspectors.

3.1.3 Regulatory Considerations

The advantage of using notebooks is that they are hardbound, with prenumbered pages. This allows for entry of raw data sequentially and in chronological order. Missing pages are obvious, as are blank spots. Therefore, from an FDA standpoint, the hardbound notebook is the most efficacious way to record raw laboratory data. Worksheets, on the other hand, have the potential for fraud, because a worksheet containing unwanted data could be destroyed and another worksheet issued in its place, leaving no evidence of the change. This possibility raises questions as to the ability of worksheets to present original raw data that are unadulterated.

An acceptable solution is to use prenumbered worksheets that are issued to the laboratory by an auditing group, such as Quality Assurance. Each worksheet contains a unique, sequentially generated number and is signed off as it is issued by the auditing group. Should a worksheet become damaged or destroyed, the auditing group would generate a replacement having a different number and document the replacement, including the number of the original worksheet and the reason for its replacement. Worksheet number generation should be done by a computer using validated software.

3.2 TASK-ORIENTED WORKLOAD

This technique can be applied to most analytical operations to some degree but is most applicable to large volume operations such as the quality control laboratory, particularly when applied to raw material control.

3.2.1 Serial Workload

In a situation where large numbers of samples are to be processed, each having many similar tests, there are two ways of handling the workload: the serial mode or parallel mode. The serial mode involves doing one sample at a time to completion. As an example, suppose a raw material sample of nitric acid was submitted for testing as per a USP/NF monograph. The sample would require clarity, identification, residue on ignition, chloride, sulfate, arsenic, heavy metals, iron, and assay. Each of these tests would be done in sequence, setting up for each test, such as arsenic and heavy metals, as needed. When all the tests are completed, a final report and sample disposition is issued, then the next sample is addressed. The workload is sample oriented, i.e., work is processed one sample at a time.

3.2.2 Parallel Workload

Suppose that, in addition to the nitric acid raw material, there are 10 other raw material samples awaiting analysis. It is likely that these 10 raw materials have many tests in common, such as arsenic, heavy metals, and residue on ignition. Using the concept of self-contained paperwork, i.e.,

using worksheets, 10 or more worksheets, one for each sample, could be carried on one clipboard. Then, the arsenics could all be done at once for each sample requiring that test. Similarly, each test that is common to more than one sample is run at the same time for each of the samples under test. As each common test is completed, the results are entered onto the worksheets for the samples requiring that particular test. The paperwork has now been consolidated, and the increased efficiency of using one setup for common tests, applied to multiple samples, results in much greater efficiency compared to using hardbound notebooks and/or the serial mode of analysis. After all the common tests are completed, the next step is to deal with parallel tests that are similar but not identical.

For example, if 5 of the 10 raw material samples require assay by titration, all of the sample weighing could be done at once, as well as the preparation for the actual titration. After all of the identical and similar tests have been completed, tests that are sample specific can be done. After all testing has been finished, the worksheets will have already been completely filled out, resulting in labor savings by reducing the time spent preparing final reports or analysis sheets. The work is documented as it is completed, rather than reviewing all the data at the end of the analysis and then transcribing it.

Task-Oriented Workload works. It saves time and results in dramatically increased productivity over sequential or sample-oriented techniques. Although this technique is most effective in quality control and other high volume laboratories that do repetitious sample analyses, it can also be applied in other areas such as R&D methods development groups. The key is to identify common activities among several different samples or projects and to execute those common activities across all those samples or projects in a concurrent manner. This technique is one to which some analysts have trouble adjusting at first, but once this technique is practiced and mastered, the results are quite impressive.

3.2.3 Sample Work Plan

The sample work plan shown in Table 3.1, presented in tabular form, demonstrates the use of parallel workload, when applied to the following USP drug substances (active ingredient raw materials), using tests specified in USP 23 monographs:

- Aluminum hydroxide
- Aspirin
- Chlorothiazide
- Dopamine HCl
- Imipramine HCl
- Metaproteranol SO_4
- Phenylalanine
- Pseudoephedrine HCl

Each of the above drug substances is listed in Table 3.1. Identical tests are arranged in columns to illustrate exactly which tests can be done in parallel. Such a work plan is useful in that it provides a complete, single-page picture of the current workload.

Table 3.1. Drug Substances Parallel Work Matrix

$Al(OH)_3$	IR	pH	Chloride	Sulfate	HM	As	
Aspirin	IR		Chloride	Sulfate	HM	As	ROI
Chlorthiazide	IR	LOD	Chloride		HM	OVI	ROI
Dopamine HCl	IR	LOD	Chloride	Sulfate	HM		ROI
Imipramine HCl	IR	LOD			HM	OVI	ROI
Metoproteranol Sulfate	IR	pH		Sulfate	HM	OVI	ROI
Phenylalanine	IR	LOD/pH	Chloride	Sulfate	HM	As/OVI	ROI
Pseudoephedrine HCl	IR	LOD/pH				OVI	ROI

IR = ID by infrared spectroscopy
LOD = Loss on drying
HM = Heavy metals
As = Arsenic
ROI = Residue on ignition
OVI = Organic volatile impurities

In some cases, such as that in the column containing pH and loss on drying (LOD), two parallel tests are listed. Four of the drug substances shown can have pH run in parallel, and five of them can have LOD run concurrently.

3.3 SUPPORT SYSTEMS

Most analytical laboratories are part of a business operation, and as such, the laboratory itself must be run as a business, taking into consideration such factors as efficiency and cost control.

3.3.1 Typical Laboratory Operation

The daily activities in the typical analytical laboratory might consist of the following:

- Chemical analysis of samples
- Preparation of solutions
- Standardization of volumetric solutions
- Inventory control and ordering of supplies
- Glassware washing
- Equipment maintenance and/or calibration
- Logging in samples
- Sampling of materials
- Methods development

The only activities that should be performed by chemists are actual analysis of samples and methods development. These activities require the skills of a chemist. Everything else should be handled through support systems. Many laboratories, especially those in smaller companies, tend to have chemists doing everything, which for a small operation may or may not be cost effective. However, in larger laboratories, support systems are essential.

These support systems consist of stock clerks for inventory control and supplies acquisition, plus laboratory aids who clean glassware, prepare and standardize solutions, and attend to basic instrument maintenance and calibration. Depending on the size of the laboratory, the jobs may be combined or separate. The use of support systems, such as laboratory aids, makes good sense in terms of both productivity and economics, but justification to upper management is often difficult. The best way to sell an idea is to show how much money it will save.

Some non-technical managers seem to think that scientists are magicians who get things done in the lab by simply pressing a button and then waiting for the results to fall out on the floor. This author once witnessed a situation where a difficult analysis was needed to release a product for shipment, and actually heard a production supervisor say to the laboratory supervisor, with great conviction, "Just shoot the sample into the instrument and give me the results." He had no idea of what is involved in performance of chemical analysis or how long it really takes to do those analyses.

Production managers need good service from the laboratory in the form of timely analytical results. The use of support systems is an excellent, cost-effective means of improving efficiency, but must be justified, often to managers of other departments who have no real understanding of laboratory operations. With this in mind, consider the cost analyses in Tables 3.2, 3.3, and 3.4.

Laboratory #1 has 30 hours of labor being applied to analytical work that does not require the skills and training of an analytical chemist or technician. The cost of lost analytical time in this laboratory

Table 3.2. Cost Analysis for Laboratory #1

Function	Salary/Year	Cost per hour	Cost per week
Chemist	$50,000	$24.04	$961.54
Chemist	45,000	21.63	865.38
Chemist	41,000	19.71	788.46
Chemist	38,000	18.27	730.77
AVG of CHEMISTS	43,500	20.91	836.54
Technician	28,000	13.46	538.46
Technician	28,000	13.46	538.46
AVG of TECHS	28,000	13.46	538.46
GRAND AVERAGE	38,333	18.43	737.18
		TOTAL	$4,423.07

Table 3.3. Cost Analysis for Laboratory #2

Function	Salary/Year	Cost per hour	Cost per week
Chemist	$50,000	$24.04	$961.54
Chemist	45,000	21.63	865.38
Chemist	41,000	19.71	788.46
AVG of CHEMISTS	45,333	21.79	871.79
Technician	28,000	13.46	538.46
Technician	28,000	13.46	538.46
AVG of TECHS	28,000	13.46	538.46
Laboratory Aid	20,000	9.62	384.62
		TOTAL	$4,076.92

Table 3.4. Weekly Operating Costs

Laboratory #1 with a new hire	$5,160.25
Laboratory #1 with overtime	$5,537.84
Laboratory #2 as is	$4,076.92

is $552.89 per week. If this time is needed in order to meet departmental or laboratory goals, the traditional solution is to hire an additional analyst or to ask the existing chemist to work overtime. If an additional analyst is hired, the salary would cost an average of $737.18 per week, making the total cost of laboratory labor $4,423.07 + 737.18 = $5,160.25 per week. With one person working overtime at time and one-half, the average cost would be $4,432.07 + (737.18 x 1.5) = $5,537.84 per week.

Laboratory #2 has a laboratory aid who performs all the glassware washing, preparation and standardization of solutions, and procurement of laboratory supplies. Since this individual works 40 hours per week, 10 extra hours of labor are available to Laboratory #2 that were not available to Laboratory #1. In addition, the chemists and technicians can spend all of their time on chemical analysis. The result is that Laboratory #2 operates at a lower cost and with greater productivity than Laboratory #1.

Laboratory #2 demonstrates the value of using support systems (in this case a laboratory aid) to manage the laboratory towards maximum productivity and quality of output.

3.4 WORK-HOUR MATCHING

Most analytical laboratories, particularly quality control and/or manufacturing support laboratories, always seem to be behind schedule, which results in workload backlogs that are usually solved by use of overtime. When the overtime becomes excessive, the laboratory manager will often try to justify additional staff. Is there a way to meet those same workload deadlines with little or no overtime and without the need for additional staff? In most cases, the answer is yes.

3.4.1 The Busy Laboratory

The first thing most laboratory managers do when their workload is continuously falling behind is throw money at the problem. How many times have laboratory managers told their bosses, "We need more instruments" or "We need more people."

This is the easy way out and will usually not solve the problem. Assuming that the techniques already described in this chapter, such as self-contained paperwork, task-oriented workload, and support systems, plus techniques that will be discussed in subsequent chapters, have all been applied with reasonable success, then look to the issue of work hour matching.

3.4.2 Cost Considerations

Manufacturing operations generally run more than five days per week. Many operations run seven days per week, 24 hours per day in order to meet sales forecasts, and because it is less expensive in

terms of overhead and energy usage to operate seven days than it is to shutdown and startup the plant every weekend. However, the analytical laboratory that supports that plant will invariably work a five-day week, typically two shifts per day. With the plant operating seven days per week, three shifts per day, it is not surprising that the laboratory workload is constantly behind schedule. Operating budgets in many companies seem to skimp when it comes to the analytical laboratory, especially in terms of staffing; therefore, the mismatch in work hours between manufacturing and the laboratory is not at all surprising.

Competitiveness in the global marketplace of today has driven companies to operate at the lowest possible cost. Justification for additional staff and/or equipment may not be well received by those who control the company checkbook. This leaves us with no other recourse than to solve the workload backlog, not by throwing money at the problem, but by managing the problem through maximization of existing resources.

Keep in mind that a company has the right to manage. This applies to both union and non-union environments. Part of this right to manage is the right to set hours of work and to prepare work schedules. In light of this, consider the following worst case scenario:

A laboratory that supports a seven-day, 24 hour manufacturing operation runs five days per week, two shifts per day. Assuming that this particular laboratory has six analysts on the first shift and two analysts on the second shift, the workload will pile up during the week and will most likely be at its worst on Monday mornings. The lab manager, in order to meet the service demands required of the laboratory, schedules as much overtime as possible, but the laboratory analysts sometimes refuse weekend overtime. Another factor to consider is that the number of samples that can be run during the week (Monday–Friday) is limited by the number of analytical instruments.

3.4.3 Getting It Right

This all too familiar dilemma can be solved by exercising the right to manage. The problem is one of work-hour mismatch between manufacturing and the laboratory. Every Saturday and Sunday, while the plant is producing and generating samples, the laboratory instruments are sitting idle or are used minimally on an overtime basis, resulting in poor efficiency and high operating cost. A simple solution, one that has been used by this author with great success at several large companies, is to stagger work hours. Rather than assigning all six analysts on the day shift to work Monday through Friday, the laboratory manager could schedule two analysts to work Monday through Friday, two analysts to work Tuesday through Saturday, and two analysts to work Sunday through Thursday. This staggered schedule becomes the regularly scheduled work week for each pair of analysts, and since the work week is the same length as before (40 hours), no overtime is paid for weekend work. The second shift remains on a Monday through Friday schedule.

Now there is a schedule that utilizes the laboratory facilities seven days a week. Work is spread out more evenly during the entire week, rather than having a glut of samples to face each Monday morning. This distribution of labor works quite well, and while many analysts may be skeptical at first about this type of schedule, many will enjoy having a weekday off as part of their "weekend." An added benefit is that overtime will either be eliminated or greatly reduced. This technique is good for both productivity and for the budget. It is suggested that at least two analysts be assigned to a shift for reasons of safety and that different pairs of analysts be rotated through the schedule so that everyone has a fair chance to sample each of the three shifts.

What if no one wants to work this schedule? Assign it by asking for volunteers on the basis of seniority, and then assign unfilled spots by reverse seniority. The example given here is based on a six-person day shift. A staggered hour plan for any particular laboratory will of course depend upon the individual staffing of that laboratory. Be creative and experiment with combinations that work for your situation.

3.5 SAFETY/HOUSEKEEPING AWARENESS

Safety awareness and housekeeping are vitally important to the productivity and attitude of workers. In the laboratory, a pleasant, safe, and well-organized environment is crucial to its success.

Safety and housekeeping go hand-in-hand. Laboratory safety inspections look at such things as housekeeping considerations, such as clutter in hoods, storage areas, and benchtops, plus accessibility to fire extinguishers, eyewashes, and deluge showers. A neat, clean work area is an essential part of a safe laboratory environment.

A clean, neat laboratory will result in better employee attitude. A lab that looks like a medieval dungeon (they do exist) with poor lighting, clutter, and dreary colors will foster poor productivity and negative feelings about working conditions. If this is combined with a weak or nonexistent safety program (as is usually the case), the result is a sloppy, inefficient laboratory with analysts who are unhappy and frustrated with their situation. This makes the manager's job impossible.

On the other hand, all other things being equal, a clean, well-lit laboratory that is spacious and pleasantly color coordinated, and which has an aggressive safety program, will show maximum productivity and positive employee attitude.

When a new laboratory is built, the design should include the considerations of adequate space, proper safety controls, and ergonomics in terms of color schemes, lighting, arrangement of benches, isles, hoods, storage space, and desk areas. In an existing lab, try renovation of hoods, rearrangement of storage space, removal of clutter and a new paint job using pastel colors such as light green, light blue, or beige to replace the traditional grays and dark greens.

Once good housekeeping is achieved, it is easily maintained through mechanisms such as regular time allocation for cleanup. Each day for example, work might stop 15 minutes early to allow for cleanup. In addition, one day a week, perhaps Friday, should include a longer cleanup period of 30 minutes or more. This will assure that employees have, and continue to have, pride in their laboratory, and most important, they will develop a sense of ownership.

A good safety program that includes employee safety awareness incorporates such elements as a written safety program, organization of an employee/management safety committee, regular safety meetings, and regularly scheduled safety training. The goal is to create a level of awareness that makes every laboratory worker an on-the-job safety inspector.

The real key to success in generating and maintaining good safety and housekeeping awareness lies with the laboratory manager. He or she must set, by example, the standard for laboratory behavior with regard to safety and housekeeping.

No phase of the laboratory operation is more important than safety. Not only is safety important, it is the law. All laboratories must comply with OSHA standards for safety, as well as those cited in regulatory documents. The United States Pharmacopeia *(USP 23/NF18, Page 7, Procedures, Paragraph 2)*, defines safety considerations that are to be applied to assay or test procedures in the Pharmacopeia, which is a regulatory document for the pharmaceutical laboratory. This paragraph reads:

> In performing the assay or test procedure in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. The Pharmacopeia is not designed to describe such hazards or protective measures.

To reiterate, not only is safety smart, it's the law. Every laboratory must comply with the OSHA Laboratory Standard (see Chapter 8). Safety and safety awareness are a way of life. Practice it diligently, and strive to achieve zero accidents.

REFERENCES

USP 23/NF 18, 1995, Rockville: United States Pharmacopeial Convention, Inc.

STANDARD OPERATING PROCEDURES

CHAPTER 3: EFFICIENCY AND SAFETY

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Notebook and Worksheet Management**	NUMBER: **003**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 5
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for the issuance and use of laboratory notebooks and worksheets.

2.0 SCOPE:

2.1 All laboratory personnel or support personnel who use laboratory notebooks and/or worksheets for data entry, calculations, and recording of results.

3.0 RESPONSIBILITY:

3.1 Quality Assurance/Quality Control/Laboratory Management, Computer Department (MIS), and Document Control.

4.0 FREQUENCY:

4.1 Each use or issuance of a laboratory notebook or worksheet.

5.0 PROCEDURE:

5.1 Notebooks

5.1.1 Issuance and Return

5.1.1.1 All laboratory notebooks must be hardbound with consecutively numbered pages.

5.1.1.2 Notebooks are to be issued from a centralized source, such as Document Control or Quality Assurance.

5.1.1.3 Each notebook that is issued must be numbered. The numbers should be consecutive and kept in a laboratory notebook log that contains book number, to whom issued, issued by, and date for each notebook.

5.1.1.4 Upon receipt of a laboratory notebook, the recipient should write his or her name and date of issuance on the inside cover, using black ink.

5.1.1.5 Upon completion of a laboratory notebook (book is full), it must be returned to the issuing source. The issuing source will enter the notebook number and date returned into the laboratory notebook log.

5.1.2 Laboratory Notebook Entries

Laboratory notebook entries are to be made in BLACK INK ONLY and shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

5.1.2.1 A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

5.1.2.2 A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establishes that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.

5.1.2.3 A statement of the weight or measure of sample used for each test.

5.1.2.4 A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

5.1.2.5 A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

5.1.2.6 A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

5.1.2.7 The initials or signature of the person who performs each test and the date(s) the tests were performed and the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

5.1.3 Errors

5.1.3.1 If an incorrect entry is made into a laboratory notebook, whether it is typographical or a correction of data, the correct procedure is to

Cross out the incorrect entry by drawing a single line through it. Never use erasers or correction fluids to obliterate notebook entries. A single line allows the old entry to be seen and read.

Write the correct data above the old and *initial and date* the new entry.

If the reason for the change is not obvious, write a *brief explanation* as to why the change was made. Initial and date the explanation.

5.1.4 Notebook Pages

5.1.4.1 Notebook pages are never to be torn out of a notebook. Unused portions of a page are to be negated by crossing out the unused portion with a large "X," made with black ink.

5.1.4.2 Pages not used should have the statement "Left Intentionally Blank" written across them in large letters and be crossed out in black ink, using a large "X."

5.1.4.3 Never write data on scraps of paper or loose pages. All raw data must be recorded in an official laboratory document, such as a notebook or worksheet.

5.2 Laboratory Worksheets

5.2.1 Issuance and Return

5.2.1.1 All laboratory worksheets must be unique, consecutively numbered entities.

5.2.1.2 Worksheets are to be issued from a centralized source, such as Document Control or Quality Assurance.

5.2.1.3 Each worksheet that is issued must be numbered. The numbers should be consecutive and generated by computer software that has been validated for this task. The system security must be such that NO TWO (2) WORKSHEETS BEARING THE SAME NUMBER CAN EVER BE ISSUED. A laboratory worksheet log should be kept that cross-references worksheet number and sample or product ID, and that contains to whom the worksheet was issued, issued by, and date for each worksheet.

5.2.1.4 Upon receipt of a laboratory worksheet, the recipient should write his or her name and date of issuance on the worksheet in the spaces provided, if any.

5.2.1.5 Upon completion of a laboratory worksheet (all blanks filled in, data entered, and raw data instrument printouts such as chromatograms and spectra attached), it must be attached to the batch record of its corresponding sample (product for example) as a permanent record of analytical activity on the subject sample.

5.2.2 Laboratory Worksheet Entries

Same guidelines apply as for laboratory notebooks.

5.2.3 Errors

Same guidelines as for laboratory notebooks.

5.2.4 Worksheet Pages

5.2.4.1 Worksheet pages are never to be discarded. Unused portions of a page are to be negated by crossing out the unused portion with a large "X," made with black ink.

5.2.4.2 Pages not used should have the statement "Left Intentionally Blank" written across then in large letters and be crossed out in black ink, using a large "X."

5.2.4.3 Never write data on scraps of paper or loose pages. All raw data must be recorded in an official laboratory document, such as a notebook or worksheet.

5.2.5 Worksheet Replacement

In the event a laboratory worksheet is damaged or destroyed, and must be replaced:

5.2.5.1 Document the destruction or damage in writing.

5.2.5.2 Ask the issuing group or authority for a replacement worksheet.

5.2.5.3 The issuing group should issue a new worksheet, having its own unique number, but which is cross-referenced to the original, with an explanation of why a new worksheet was issued.

5.2.5.4 The new worksheet is to be stored with the batch record for its sample along with the written explanation of how the original worksheet was damaged or destroyed. The explanation serves as a destruct notice.

5.3 Chromatograms, Spectra, and Other Instrument Readouts

5.3.1 For laboratory worksheets, instrument readouts can be attached directly to the worksheet and filed with batch records for the material that was tested.

5.3.2 For laboratory notebooks, instrument readouts can be stored in separate looseleaf binders and referenced in the laboratory notebook. In this case the referencing must be two-way. The readouts contained in looseleaf binders must reference a hardbound notebook page, and the hard bound notebook must reference the exact location of applicable instrument readouts.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Basic Laboratory Safety and Housekeeping**	NUMBER: **004**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To outline the basic requirements for laboratory safety and housekeeping.

2.0 SCOPE:

2.1 All personnel using the laboratory facilities in any capacity, including visitors.

3.0 RESPONSIBILITY:

3.1 Laboratory directors, managers and supervisors, and working analysts and laboratory support personnel.

4.0 FREQUENCY:

4.1 Continuous and ongoing.

5.0 PROCEDURE:

5.1 Any laboratory used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations.

5.2 Any such laboratory shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different samples.

5.3 The flow of samples through the laboratory shall be designed to prevent contamination.

5.4 Adequate lighting and ventilation shall be provided in all areas of the laboratory.

5.5 Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for safe and efficacious operation of the laboratory.

5.6 Sewage, trash, and other refuse in and from the laboratory and immediate premises shall be disposed of in a safe and sanitary manner.

5.7 Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas in and around the laboratory.

5.8 Any laboratory used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such laboratory shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

5.9 Any laboratory used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair. Benchtops and instrumentation should be free of dust and debris.

5.10 There should be regularly scheduled laboratory housekeeping and safety inspections, conducted by representatives of an appointed safety committee.

5.11 There must be an adequate safety and housekeeping training program in place that includes safe laboratory practices, housekeeping skills, and familiarization with hazards associated with the laboratories and how to deal with those hazards.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

CHAPTER

4

Tools of the Trade: Capabilities and Training

4.1 PASSENGER REMOVAL

In any company or organization, there are two basic types of employees: the "movers and shakers" who make things happen and get things done, and the "passengers," who just seem to be along for the ride. The laboratory is no exception and has its share of each.

4.1.1 Identification

It is incumbent upon every good manager to identify the capabilities, talents, work ethic, and professional motivations of each individual that he or she manages. Once the passengers have been identified, the manager has a duty to remove those individuals from passenger status. The first obligation of a manager is to find out why a particular individual is a passenger and then to offer the appropriate remedies, such as counseling, additional training, or efforts to accommodate any special needs of that individual. If all reasonable efforts fail, it may be necessary to consider other options, such as termination or transfer of the individual in question.

Termination should only be used as a last resort, after all other reasonable efforts have been exhausted. However, passengers must be removed in order to maintain both maximum operating efficiency and good morale among good performers. Also, it goes without saying that any matters relating to the disposition of an employee should be handled in concert with the company's Human Resources Department.

In the analytical laboratory, some common traits of a passenger are absenteeism, failure to follow written procedures, poor analytical work that must frequently be repeated by others, poor safety awareness, poor quality awareness, poor productivity, tendency towards horseplay, and apparent failure to grasp the basics of the job, as evidenced by the constant need for supervisors and managers to rehash instructions.

4.1.2 Capabilities

Capabilities of analysts can be identified through a process of review and testing. Review of laboratory results generated by an analyst over a period of time will allow a manager or supervisor to

get a feel for any patterns that develop in terms of good or bad performance. Testing by use of dummy samples or blind controls can also be used as means of evaluating analyst capability in a way that is both fair and consistent.

4.1.3 Remedies

Specific tools for defining the capabilities of lab analysts and for identification of deficiencies and for dealing with those deficiencies are presented in chapters covering the SPACE System of Laboratory Management. Training as a remedy will be discussed in this chapter.

4.2 TRAINING

The discussion of passenger removal was referring to the situation where one or two individuals (small percentage) have become an anchor to the organization and with whom management must deal. But what if many chemists are not following procedure or seem not to know their jobs? If almost everyone appears to be a passenger, then maybe the problem is with management.

4.2.1 Expectations

Employees must be told what is expected of them; otherwise, they won't know what to do. Clearly defined expectations are critically important to the performance and professional growth of any individual. For laboratory people, who tend to be logical individuals dealing with facts and data, this is especially important. If expectations are not made clear, the analysts in the laboratory will have uncertainties that could and probably will result in a laboratory whose performance is less than desirable. In this case, perhaps the manager or supervisor is the passenger.

How do managers make their expectations known, and more important, how do they follow up to make sure that those expectations have been fully understood and acted upon in a manner consistent with required performance standards? The answer is Training, Training, and More Training!

As a rule, training should account for 15 to 20 percent of an analyst's time. Aside from training or instruction that is part of new employee orientation, the laboratory professional should be given specific training in areas such as the following:

- Standard Operating Procedures for the Laboratory
- Analytical Methodology
- Laboratory Instrumentation
- Material Safety Data Sheets
- Project Goals/Workload Planning
- Communication of Scientific Information

4.2.2 Training and the Technical Trainer

The specialized technical training that is required for proper operation of a laboratory can be administered in several ways. One way is to have an informal system where the supervisor provides training during the course of the workday as needed. This learn as you go system of training is

normally not structured and is usually ineffective and inconsistent. It is recommended instead that a formal written training program be developed—one that is administered and coordinated by a single individual to whom the responsibility of technical training is officially delegated. This individual can be any knowledgeable technical professional in the organization. If a laboratory operation is large enough, it may be worth creating a full-time position of Technical Trainer. The technical trainer plans, schedules, and administers each training course. It is the responsibility of that individual to do the following:

- Develop specific training courses/seminars.
- Schedule technical personnel to attend all sessions.
- Keep attendance sheets for each session.
- Obtain feedback from each session via a seminar evaluation survey form.
- Schedule rotation of technical personnel through each session so that each individual repeats each session at regular intervals.
- Provide special training to supervisors so that they are able to reinforce the training in the laboratory on a daily basis.
- Provide centralized distribution of all technical training course materials.

The technical trainer should be a technical person but does not need to have expertise in all areas. The trainer needs to rely on a variety of technical experts to develop specific training courses or seminars. These experts could be in-house employees or could be recruited from outside the organization. A good source is vendors of laboratory instruments. The actual courses are given by experts in concert with the technical trainer. The technical trainer's primary function is to coordinate and manage the training program.

After a training session is given, it is vitally important to keep the information fresh in everyone's minds. This is best achieved as part of day-to-day supervision. The supervisor, manager, or group leader of a particular laboratory must constantly reinforce training by way of daily discussions with working analysts, and through a process of two-way dialogue that challenges the analyst and provides direct feedback to the supervisor, manager, or group leader.

4.2.3 Training as a Dynamic Process

Technical training sessions can be used to explain a new Standard Operating Procedure (SOP), an analytical technique, or problem-solving and troubleshooting techniques. Whatever the content, it is important to have a training coordinator, such as a technical trainer, regularly scheduled training sessions, follow-up training, and daily dialogue and reinforcement among technical professionals and with their managers. Consistent, ongoing training can and will result in a laboratory operation that is efficient and productive, and in which the expectations of management are clearly and consistently understood by all.

Figure 4.1 is an example of a training attendance sheet that is useful for keeping training records for formal sessions, while Figure 4.2 is a supervisor training sheet that can be used for on-the-floor training. Since it is very difficult to achieve levels of 15 percent time spent in training with formal

sessions, daily communications between supervisors and chemists, such as showing someone to use a pH meter or explaining the operation of an HPLC detector, should be classified as training and recorded as such. The form shown in Figure 4.2 facilitates documentation of this type of training.

Formal classroom training will probably account for no more than five percent of actual time spent on training. The rest will be practical training that is given by supervisors and managers during the course of the workday. The trick is to document every incidence of such training. Even the most basic interactions between supervisors and analysts can be recorded as training. Every time an analyst asks a question about some laboratory procedure or protocol, it should be recorded as training. For example, if an analyst asks, "How do you want me to handle these samples?", the answer given by the supervisor, even though the answer may only take several minutes, should be recorded as training. Every interaction between analysts and their supervisors is an opportunity for documented training.

This dynamic style of ongoing training through a continuous process of challenge and feedback is an efficient and exciting way to obtain productivity and training at the same time.

The Menus referred to in the sample training attendance sheets is a mechanism to reduce paperwork. If all training courses and/or subjects are listed alphabetically, with a different number assigned to each one, then a menu of subjects is created. When filling out an attendance sheet, the course or subject can be referred to by number. If a computerized tracking system is in place, the tracking software can convert numbers to names and vice versa.

Figure 4.1. Training attendance log.

TRAINING ATTENDANCE LOG

Date _____ Time _____

Location _____ Instructor _____

Training Course Number (from menu) _____

<< If Training Course is NOT ON MENU >>

Name of Course _____

Source (SOP, etc.) _____

NAME (Printed)	I.D. #	SIGNATURE

Figure 4.2. Supervisor training log.

Name of Supervisor _____ Date Issued _____

DATE	I.D. #	NAME (Printed)	MENU #	TOTAL TIME	SIGNATURE

STANDARD OPERATING PROCEDURES

CHAPTER 4: CAPABILITIES AND TRAINING

SOP 005: Laboratory Training

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Laboratory Training**	NUMBER: **005**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To state the basic requirements for laboratory training.

2.0 SCOPE:

2.1 Laboratory directors, managers, supervisors, analysts, and laboratory support personnel.

3.0 RESPONSIBILITY:

3.1 Laboratory directors, managers, supervisors, analysts, and laboratory support personnel.

4.0 FREQUENCY:

4.1 Upon transfer to laboratory and continuous on the job.

5.0 PROCEDURE:

5.1 Training for New Laboratory Personnel

5.1.1 Complete cGMPs.

5.1.2 Safety and housekeeping rules.

5.1.3 Laboratory Standard Operating Procedures.

5.1.4 Laboratory workflow and documentation.

5.1.5 Operation of laboratory instrumentation and apparatus.

5.1.6 Performance of analytical procedures.

5.2 Training Provided to Laboratory Personnel on a Yearly Basis after One Year of Service

5.2.1 cGMPs applicable to their individual jobs.

5.2.2 Review of major changes within the laboratory, such as new product analysis, new documentation procedures, or regulatory issues.

5.3 Training Provided to Laboratory Personnel on a Continuous Basis

5.3.1 Daily dialog with supervisors and peers.

5.3.2 Classroom training sessions.

5.4 Documentation

5.4.1 Each training session should be recorded on a training attendance sheet that specifies employee name, time and date of training, subject of training, and duration of the training session. This can be tracked either manually or by use of a computerized training tracking system. Training records should be stored in such a manner as to be easily retrieved and interpreted.

5.4.2 Each laboratory employee should keep a personal training notebook in which notes can be taken during training sessions and later referenced for review purposes.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

CHAPTER

5

Tools of the Trade: Supervision

5.1 TOTAL-IMMERSION SUPERVISION

In any laboratory, there will be either working supervisors or full-time supervisors. The working supervisor is one who must do actual benchwork in addition to the handling of supervisory responsibilities. The full-time supervisor is one who devotes 100 percent of his or her time to supervision. In the analytical laboratory, supervisory tasks are many—too many for the supervisor to also be involved in day-to-day analytical work. The laboratory supervisor's duties will include such tasks as:

- Scheduling work
- Calibration and maintenance of instrumentation
- Training
- Review and audit of data
- Monitoring of workflow on a continuous basis
- Communications with other departments
- Inventory control
- Supplies procurement
- Compliance with safety and regulatory rules

With this assortment of responsibilities, how can a supervisor also do benchwork and expect be fully effective as a supervisor? The answer is, the supervisor can't.

The real key to effective, progressive supervision is the total-immersion style of supervision. The role of the supervisor is to supervise. The supervisor in the laboratory must constantly challenge each analyst by reviewing work on a regular basis, and asking each analyst, "Why? Why? Why?" This approach may seem confrontational, but is not meant to be. If the flavor of the challenge

process is that of promoting maximum job awareness and technical knowledge, the questioning and challenging of each analyst develops a two-way dialogue that results in an environment of mutual continuous learning, clarity of expectations, and maximum productivity that is characterized by quality output with a minimum of errors.

In addition to continuous monitoring of the workflow, the laboratory supervisor must provide training and is responsible for the work of his or her analysts, which requires a serious time commitment to checking and auditing of data prior to publishing analytical results. The supervisor is also responsible for calibration of equipment, maintenance, problem-solving, compliance with written procedures, scheduling of personnel and workload, plus supplies procurement and safe operation of the laboratory. How is the supervisor supposed to find the time to do analytical work? Many companies expect the laboratory supervisor to spend as much as 50 percent of his or her time on lab work. This is one of the ways that some companies try to skimp on laboratory budgets. If the supervisor spends a significant amount of time doing lab work, the supervisory tasks will suffer which is guaranteed to result in a laboratory that is in trouble.

As a matter of personal experience, laboratories with working supervisors do not fare as well as those with full-time supervisors. The only way to go is total-immersion supervision. The cost of an additional analyst to handle the workload is offset many times over by the benefits of full-time supervision—where maximum productivity, compliance, continuous interaction, safety awareness, and consistency (avoiding the Storytelling Syndrome) are a way of life.

5.2 SWA WITH INTERCOMM

This odd-sounding title is a shorthand for "Structured Workload Assignments with Intercommunications." There are several ways that work is assigned in the analytical laboratory. One is to let everyone grab what is available (the chemist choosing the work) from a pool of analyses that need to be done. This does not work well because analysts will tend to select the easy work, or work that they like, rather than paying attention to priorities. Less pleasant tasks are left to the other guy, resulting in procrastination that leads to work backlogs and delays. Another technique is for the supervisor to give a chemist a list of things to do (usually verbal) without any formal priorities. This is another form of letting the chemist choose the work, where the supervisor is only doing half the job by letting the chemist set priorities. Both of these techniques have the effect of removing some management control from the hands of the manager or supervisor.

5.2.1 Maintaining Control

How does the laboratory manager/supervisor maintain control? The answer is structured workload assignments. A specific, written list of assignments should be given to the laboratory analysts at the beginning of each workday. This written list is provided by the manager/supervisor and consists of each analyst's name and the specific analysis or analyses that are assigned to that analyst for that day. The list could be put on a blackboard or magnetic board that is prominently displayed in the laboratory. This would serve to reinforce the concept of structured workload assignments and would act as a constant reminder to each analyst, and to the manager/supervisor, of current activity. Changes to assignments, dictated by changing priorities, are immediately posted on the board and communicated to the analysts. This way, there is never a misunderstanding about assignments or priorities;

the analysts know what is expected of them, and the manager/supervisor has appropriate control of the laboratory workload and is on top of current status at all times.

5.2.2 What Are the Rules?

What about intercommunication (Intercomm)? Who sets priorities in the analytical laboratory? We know it isn't the analyst. But what about the laboratory supervisor? Does he or she set priorities? The answer is no. The laboratory supervisor assigns work based on priorities, but does not actually set those priorities. Well then, who does?

Remembering that the analytical laboratory is a service group, serving its customers—those customers being either an actual customer of the company, or more likely, another department within the company such as Manufacturing or Product Development—it is the customer who sets laboratory priorities. As a manager or supervisor of an analytical laboratory, success is highly dependent upon four critical rules. They are as follows:

1. The analytical laboratory exists to serve its customers.
2. The customer sets laboratory priorities.
3. Laboratory work must be assigned based on those priorities.
4. Intercommunications between the laboratory and its customers must be ongoing in order to handle changing priorities and to relay status of workload to those customers.

The analytical laboratory manager/supervisor will never go wrong by following the guidelines set forth above. Rule number one (The analytical laboratory exists to serve its customers) is self explanatory. If one does not believe this, then the other rules are irrelevant, as is the manager/supervisor.

Rule number two (The customer sets laboratory priorities) is a must. Since workload coming into the laboratory usually exceeds laboratory capacity in that not everything can get done at once, it is necessary for those submitting the work to establish priorities. For example, a quality control laboratory that is supporting a manufacturing plant will need to know the work priorities that will best serve that manufacturing unit. These priorities must be set by Manufacturing management. It is the job of the laboratory manager/supervisor, at the beginning of each shift, to communicate directly with the customer, in this case plant supervision; to relay what workload is in the laboratory; and to ask for priorities based on that workload. An example of this is calling the plant manager or supervisor on the telephone at the beginning of the day and saying, "We have 10 products in the lab for analysis. Which ones do you want first and which ones can wait until later in the day?" The laboratory has now placed the burden and responsibility of decisions relating to priorities on the plant, where it belongs. This way there is no misunderstanding about what products must be serviced first, last, and so on.

The worst thing a laboratory manager/supervisor can do is to make decisions concerning prioritization of workload. The laboratory manager who does this will be blamed for any and all manufacturing delays. The laboratory must let the customer, in this case the plant, prioritize workload. If the customer says that everything is a priority (an unrealistic but very popular statement), then the laboratory manager/supervisor has to take a tougher stand and tell the customer, as an example,

"We have 10 products in the lab, but can only start five at this point. You tell me which five you want." If the customer still insists that everything is a priority, it's time to play hardball. Then the laboratory manager might say, "Well, in that case I'll have to ask your boss to help set priorities." No matter how noncommittal or unreasonable the customer might be, the laboratory manager must never give in to the temptation of setting priorities. This will result in doing someone else's job and becoming liable for decisions that are not in the domain of the laboratory.

Rule number three (Laboratory work must be assigned based on those priorities) is also self explanatory. Assigning the work is the responsibility of the laboratory manager/supervisor, using the priorities set forth by the customer as a basis for those assignments.

Rule number four (Intercommunications between the laboratory and its customers must be ongoing in order to handle changing priorities and to relay status of workload to those customers) is carried out by expanding upon rule number two (The customer sets laboratory priorities). In addition to obtaining priorities from the customer, the laboratory manager/supervisor must give an estimated time of completion for laboratory work. If a problem develops, this information must be relayed so that new priorities can be set or so that the customer can make adjustments to his or her operation based on updated completion time estimates. A sample scenario might be, "The HPLC broke down, and since it will take about two hours be up and running, we won't have the results of your analysis until 4:00 PM, instead of 2:00 PM as originally estimated." The intercommunication with the customer involves two things. One is to get priorities from the customer, and the other is to communicate completion commitments and the status of those commitments on an ongoing basis.

Following the four basic rules set forth above, the laboratory manager/supervisor will be in control of the workload and will have established the communications with the customer that is needed to provide proper service without misunderstanding or loss of productivity.

5.2.3 Teamwork Approach

We can summarize this point by restating the proper QC Laboratory/Manufacturing relationship. For QC, daily contact with Manufacturing is a must. QC must ask Manufacturing, *every morning*, what are the priorities? If a conflict exists or a result is going to be delayed due to problems, Manufacturing must be told as quickly as possible so *they* can rearrange the priorities. QC will run more smoothly, and without conflict, if the burden of decision regarding workload priority is consistently with Manufacturing, where it belongs. The main responsibility of QC is to communicate on a timely basis.

5.3 INTERLABORATORY EFFICIENCY MATCHING

An area of planning that should be obvious, but often is not, is that of interlaboratory efficiency matching. What does this mean?

5.3.1 Corporate Geography

Companies are arranged in one of two ways where analytical laboratories are concerned. Either the R&D labs and the QC labs are at the same location or at different locations. They usually operate out of different cost centers, which means that they have separate budgets and planning strategies. R&D labs and QC labs often order equipment and instruments that are different. But since R&D

usually develops methods that are subsequently transferred to QC, having different equipment often leads to gross inefficiencies within both labs. Let's look at an example of how this happens.

5.3.2 Technology Pipeline

If R&D develops a method by HPLC and transfers it to QC, it should work as written, provided ruggedness has been established. But ruggedness studies are often done on R&D equipment, and when the method is attempted by QC personnel, it (the method) may not perform as predicted due to some feature or idiosyncrasy of the QC instrumentation, or because of a difference in brand or lot number of HPLC column for example. This results in extra work and lost time, committing both R&D and QC resources towards solving a problem that should have never arisen, and is particularly distressful if the R&D and QC labs are at different geographic locations. It is a common problem. How many times has a QC Manager told the R&D Department, "Your method doesn't work"? This kind of situation does nothing but diminish the credibility of both R&D and QC and creates friction between them. How then does one do it right the first time?

5.3.3 The Planning Solution

Laboratory planning must be a global activity. The managers/directors of all laboratory groups need to confer on equipment planning so that R&D and QC have the same types and brands of instrumentation. This will facilitate methods transfer and, as an added bonus, lower costs for spare parts and service contracts. Where chromatography is concerned, when R&D develops a method, it should transfer not only the method, but the actual chromatography column as well. In the case of HPLC, one can reserve the lot of packing used in the column upon which the method was developed. This will give some long-term insurance that the separation will continue to work from column to column. As the stock of packing gets low, R&D has time to develop the separation on a new lot for future use. GC columns are more reliable in terms of reproducibility and can be ordered as needed. The transfer of a column to QC will facilitate method transfer by allowing the QC personnel to participate in ruggedness testing of a new method. Both labs run smoothly, credibility remains high, and cooperation between R&D and QC is maximized since they are now involved in an active and productive partnership.

5.4 ACCELERATED PROBLEM-SOLUTION LOOP

Analytical laboratories must produce accurate results in an efficient and timely manner. Workload planning and schedules are designed to meet a variety of daily deadlines, which are prioritized through ongoing communication between the laboratory and its customers.

5.4.1 Things Happen

What happens when something goes wrong? What happens, for example, when an HPLC pump blows a seal or a detector lamp burns out in the middle of a run or an instrument breakdown occurs? Suppose analytical results are erroneous or out of specification. These are examples of situations that can slow down laboratory output. Someone has to address the problem before work can resume its normal course. In a situation like this, who should be responsible?

5.4.2 Who Solves the Problem?

In an R&D environment, schedules are generally flexible enough that a glitch in the workflow will not have much of an impact one way or the other. But in a high-volume, high-pressure analytical

laboratory, such as a QC or a production support operation, a work slowdown can be more than just inconvenient.

In such an environment, analysts should notify the supervisor *immediately* when a problem develops. This allows the supervisor to decide whether the chemist's workflow will remain as is or will be channeled to other activities while the supervisor works on the problem. In these environments, the analyst must produce without being sidetracked by problems that the supervisor can address. The supervisor, if he or she is practicing total-immersion supervision, is better equipped to handle adverse situations that can and will develop over the course of any given day. Training of analysts to handle many of these problems can be done during time set aside for structured training, but the actual flow of work should never be compromised.

Even when an analyst is trained to handle the problem at hand, the supervisor should be notified so that he or she can make the actual decision as to how the problem will be addressed. In addition, timely notification of the supervisor facilitates communication between the lab and its customers, should a delay of deadline be anticipated. The lab will have a structured problem-solving system that can only serve to enhance the overall credibility of that laboratory as a reliable service group.

5.5 COMPUTERIZED TRACKING

One of the most time consuming tasks for the laboratory manager is that of tracking current workload. This activity, if done manually, is fraught with opportunities for error, i.e., overlooking samples, resulting in delays for the laboratory's customers. Large volume labs are particularly vulnerable. The analytical laboratory must be able to manage its workload reliably without worrying about missing samples or miscued priorities.

5.5.1 Keeping Track of It All

One way of insuring reliable sample/workload tracking is to use some form of computerized workload management. Today's low prices on personal computer systems makes this capability available to any analytical laboratory operation.

An example is a PC-based software package that allows log-in of samples into the laboratory and gives the lab manager instant information, such as current active workload in reverse chronological order plus data on what has been released or deleted.

On the following page is an example of how a low-cost PC-based package can meet most laboratory sample tracking requirements. Sample menus are shown here for illustrative purposes.

The main menu screen shown offers six selections. Each has a specific sample handling or reporting function.

Selection <A> Log-in allows samples of all kinds to be entered into the system. Selection <B> Release is used to release a material to Manufacturing or some other department, such as R&D. Selection <C> Abort simply allows removal of samples from the system. These three functions should be interrelated. Whenever a sample of any kind, such as a raw material or finished product, arrives in the laboratory, it is good practice to log it into the lab system as soon as possible to give

Figure 5.1. Sample management system—Master select menu.

CODE	PROGRAM	FUNCTION
<A>	LOG-IN	Log Sample(s) into System
<B>	RELEASE	Release Materials as Approved
<C>	ABORT	Remove Sample(s) from System
<D>	REPORTS	Sample Processing Queries
<E>	UTILITIES	Program Utilities
<X>	EXIT	Exit Software

Press Code to Select Function

it a unique identification and to label it with that identification. The Log-in function in this example is designed to handle this in a manner consistent with GMPs and GLPs.

What is a sample release? The time when testing is complete on a sample, and the results are reported to the submitter of the sample. The sample may be a finished product that is actually released for shipment, a raw material that is released for use by Manufacturing, or an in-process or research sample. The release function should do two basic things. First, it should remove samples from the system. Second, and more important, for finished products, it should store a permanent record on a mass storage device, such as a hard disk, of the sample lot number and the date it was released.

Selection <D> Reports invokes a separate reports sub-menu which offers a variety of workload and sample status reports. Selection <E> Utilities invokes a software utility menu, and Selection <X> Exit returns the computer to its operating system.

The sample Reports section should provide a hard copy of the laboratory's entire sample workload by dates and/or sample types. Samples might be printed out in reverse chronological order, for example, to facilitate management of samples on a first-in, first-out basis. The printed report should include all sample data, plus spaces to jot in assignments by analyst or by priority.

In addition, screen displays need to be available that show the status of any particular sample, the release date of any finished product that was previously released, and a daily summary of all finished product samples released on any particular day. A means should be provided for rapidly finding the date on which a finished product was released, and the quick search which does away with hunting through files techniques, is particularly useful when rapid information is needed for a customer or regulatory agency. The on-screen review of all finished products released on any particular day can be useful for in-house communications between QC/QA and Manufacturing or as a lab productivity indicator.

Figure 5.2. Sample master select menu for reports.

CODE	FUNCTION
<A>	Print Sample List
<B>	Sample Status Query
<C>	Release Date Query
<D>	Daily Release Summary
<X>	Exit to Main Menu

PRESS CODE TO SELECT FUNCTION

5.5.2 A Variety of Solutions and Options

Regardless of what kind of software package is selected or how sophisticated it may be, it should have log-in and release functions as a bare minimum. One of the best ways for a laboratory manager to help himself or herself is to be to know the current status of the workload at all times. The old line, "I don't know, but I'll get back to you" only works if used sparingly. A manager who is perceived as knowledgeable and consistently well-informed is a manager who will be well thought of and respected by members of his or her organization.

STANDARD OPERATING PROCEDURES

CHAPTER 5: SUPERVISION

SOP 006: Laboratory Workload Management

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Laboratory Workload Management**	NUMBER: **006**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide general guidance for handling workflow through the laboratory, and to state general requirements for testing and release of raw materials, in-process materials, and finished products.

2.0 SCOPE:

2.1 Laboratory directors, managers, supervisors and analysts, plus Quality Assurance and Production management personnel.

3.0 RESPONSIBILITY:

3.1 Laboratory directors, managers, supervisors, and analysts in concert with Production management.

4.0 FREQUENCY:

4.1 Daily, ongoing.

5.0 PROCEDURE:

5.1 General

5.1.1 Samples are to be brought to the laboratory by personnel responsible for taking samples and delivered to a central laboratory incoming sample location. All samples must be properly labeled.

5.1.2 Sample must be signed in, using a sample log book into which is written the sample name, lot or batch number, number of containers, date sampled, time delivered to the laboratory, and the name and initials of the sampler. Separate log books should be kept, one for raw materials and another for in-process and finished product samples.

5.1.3 A laboratory manager or supervisor should check the incoming sample log books on a regular basis throughout the work day.

5.1.4 If laboratory worksheets are used instead of notebooks, the laboratory must notify the central issuing authority of all new sample receipts in order for worksheets to be issued on a timely basis for each sample.

5.1.5 Laboratory management should communicate the workload to Production management at regular intervals (such as beginning, middle, and end of shift) in order to establish workload priorities.

5.1.6 Work should be assigned based on those priorities.

5.1.7 Laboratory management and Production management must maintain ongoing communications in order to relay status reports on progress of analytical work and to make known any problems that might cause delays or result in a change of priorities.

5.1.8 Upon completion of a sample, the data for that sample are to be audited. If all raw data, calculations, and results meet acceptance criteria, then the sample results may be published. If there are problems or errors discovered during the auditing process, an investigation must be conducted in order to correct the problem and to arrive at a suitable sample disposition.

5.1.9 Upon completion of a sample, the date of completion should be entered into the sample receipt logbook, along with the initials of the laboratory analyst or analysts who performed the analytical work on that sample, thereby closing out the entry for that sample.

5.2 Quality Assurance

5.2.1 Run a control sample with each analysis as a check on the method and equipment.

5.2.1 Submit a blind control sample to analysts on a random basis, such as once every 10 assays, as a check on the analysts.

5.2.2 Document the results of control samples and compare them to the historical statistical data for that sample.

5.2.3 Treat control sample data as described in SOP 039, "Preparation and Use of Control Samples."

5.3 Failure Investigations

5.3.1 For any out-of-specification analytical result, an informal laboratory investigation must be performed in order to either accept or overcome the failing result. Refer to SOP 033, "Laboratory Failure Investigations."

5.4 Documentation

5.4.1 All analytical work on any sample must be thoroughly documented either in a laboratory notebook or on a laboratory worksheet. All raw data, including chromatograms and spectra must be included.

5.4.2 All data for any particular sample analysis must be easily retrievable upon request.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

CHAPTER

6

Tools of the Trade: Geography and Technology

6.1 GEOGRAPHY AND TECHNOLOGY

Two of the largest obstacles to good laboratory efficiency are the state of technology in the laboratory and the geographical layout of the laboratory. Looking first at geography, many laboratories are designed without the chemist in mind. Equipment is often arranged in what seems to be a logical pattern, such as a wet lab that is segregated from an instrument lab, but that does not necessarily lead to maximum efficiency. Equipment and apparatus should be organized according to the type of work or by major tasks, rather than by equipment grouping alone. The examples of laboratory layouts, shown in Figures 6.1 through 6.3, provide a good view of how laboratory geography and technology can be utilized effectively.

Figure 6.1 is especially interesting. Even though this is an example of a QC lab that was used to test both pharmaceutical and non-pharmaceutical samples, it is presented here and discussed in great detail, because it is one of the finest examples this author has ever witnessed of how changes in both geography and technology can have a major impact on laboratory efficiency and efficacy.

Many Tools of the Trade are utilized in the resolution of laboratory problems related to geography and technology.

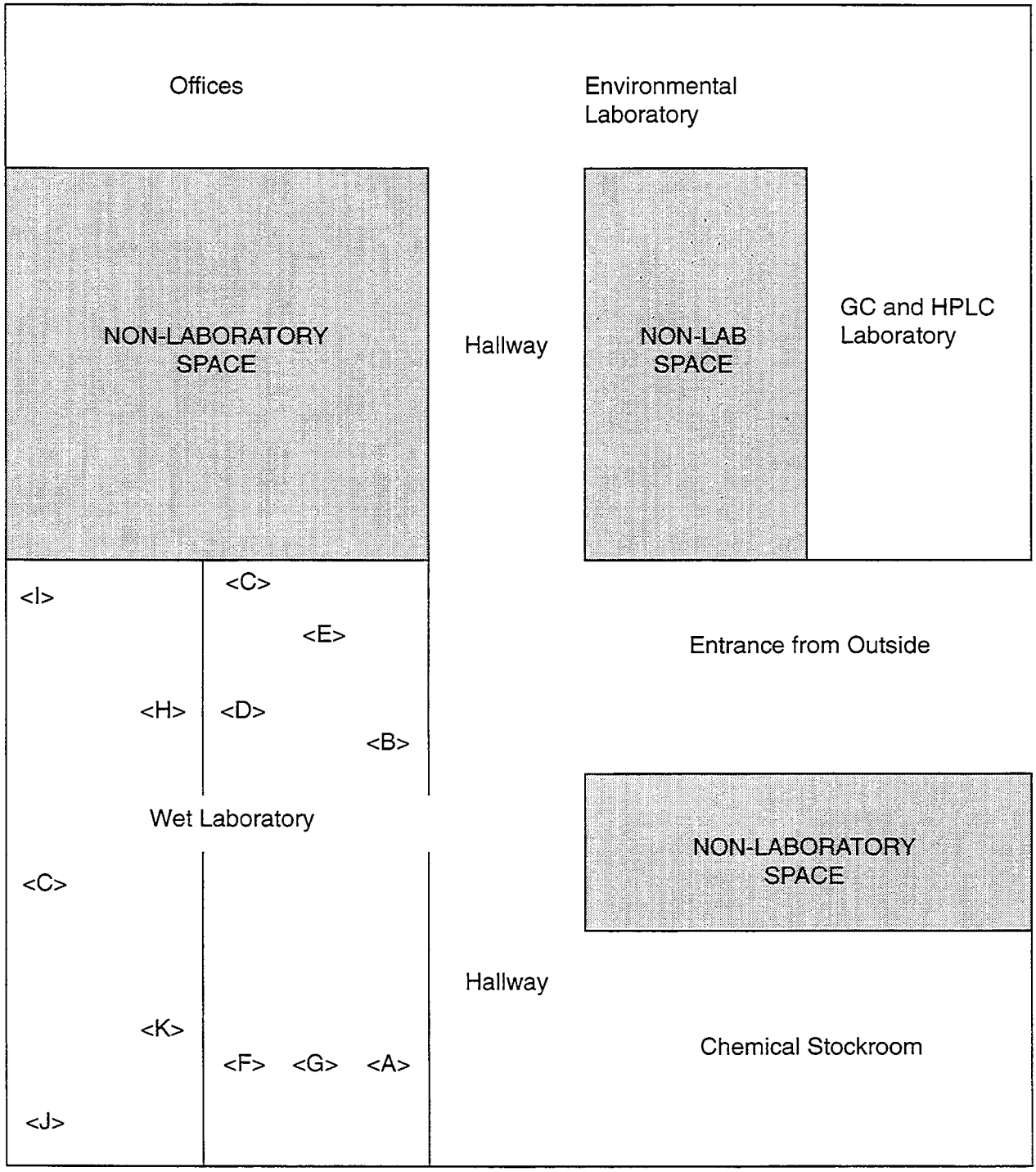
6.1.1 A Poor Example

Figure 6.1 is a classic example of how unplanned evolution can result in poor organization and low efficiency. This floor plan is an actual example of a quality control department to which major improvements were made by using some of the management techniques described in this chapter.

The portion of the building that housed the wet lab was built in the 1940s and remained essentially unchanged for about 20 years. The other half of the building, containing the office and environmental and chromatography labs, was added on in the 1960s.

This lab supported a chemical plant that manufactured organic intermediates, such as amino acids, liquid esters, and cyano compounds, many of which were pharmaceutical raw materials or precursors.

Figure 6.1. An example of poorly organized laboratory space.



Solid products such as phenyl glycine and cyanoacetic acid were tested using wet chemical techniques such as titration, nitrogen distillation (modified Kjeldahl), and derivatizations such as oxime formation. All of these techniques were either labor intensive and/or lacked specificity. The liquid products and most raw materials were tested by gas chromatography, using area normalization. The chromatographs were fairly old and in a constant state of disrepair. Most of the instruments did not even have proportional control of oven temperature. Work assignments were such that analysts were constantly marching back and forth between the wet lab and chromatography lab with samples. In addition, QC analysts were responsible for doing the wastewater analyses in support of the wastewater treatment plant. This testing was done in the environmental lab.

Looking at the arrangement of equipment in the wet lab, the letters A-K represent the following:

<A> Sample storage and sample sign-in area.

<B> Titration benches and analytical balance.

<C> Fume hood.

<D> Titration bench and sample prep space.

<E> Center island filled with nitrogen distillation units.

<F> Sample prep space.

<G> Center island used for paperwork and polarimetry.

<H> Water still and glassware washing.

<I> Drying ovens and desiccators.

<J> Automatic titrators.

<K> Stirring plates and specialty testing.

Samples were signed into the lab and placed on a storage shelf for assignment to one of the analysts. Assignments were made on the basis of location, i.e., one or two analysts were assigned to the chromatography lab, one to the environmental lab, and one or two to the wet lab, depending on workload. Since samples were signed in (one 4-oz bottle of each) to one location, and since some samples required both wet tests and chromatography, the moving of samples between labs was extensive. Samples had to shared by several analysts, resulting in a significant amount of traffic by analysts going from lab to lab delivering samples to each other. In addition, the analysts had to go to the plant to collect samples. The layout of the lab and the sharing of samples led to a lot of unnecessary footwork and wasted time. Also, the state of technology in the laboratory was such that the level of skill, coupled with a furious workload, compromised the credibility of the laboratory, which was under constant criticism from Manufacturing in terms of data reliability. Finally, this QC group had six analysts to cover two shifts in support of a seven-day, 24-hour plant operation. The workforce was unionized and often refused weekend overtime, resulting in enormous backlogs every Monday morning. Compounding the problem was the fact that analysts were selected by seniority from the general union population in the plant, whose members had no lab experience or knowledge of chemistry, and therefore needed modern, automated lab equipment that produced accurate data with minimum dependence upon analyst technique or interpretation.

In terms of equipment, the balances were manual, single-pan types, all nitrogen distillation units were manual, only one auto-titrator was available, and the gas chromatographs were antiquated by the standards of the day. Documentation was extremely ill-considered and cumbersome to use. This department had evolved naturally into a first rate disaster. How was this lab turned around to become one of high skill, efficiency, and credibility? Let's look at the changes that were made and how they impacted on the QC operation at this plant.

6.1.2 Major Changes, Before and After

In the area of technology improvements, the goal was to increase efficiency and accuracy. Since level of skill among analysts was a problem, it was also necessary to focus on reducing subjective measurement by maximizing automation and improving training in basic technique. It was first noticed that weighings took an inordinate amount of time. Analysts were weighing accurately to exact numbers, i.e., if a step called for an analyst to "accurately weigh about 1 gram of sample," it would be weighed out to 1.0000 grams. Since single-pan manual balances were being used, a weighing seemed to take forever.

The analytical balances were replaced with electronic balances that had digital readout and automatic tare. The analysts were retrained on weighings to understand that an accurate weighing means that one needs to record the weight accurately, but need not weigh the exact amount specified. In another words, a weighing of 1 gram could be anywhere from 0.9 to 1.1 grams as long as the exact weight was known. The result was a five-fold decrease in weighing time per sample.

The next project was to reduce the amount of time spent doing nitrogen distillations through the use of automation. The existing setup consisted of six manual distillation stations, each containing a boiling flask, a West condenser, a delivery tube off the condenser, and a receiving flask. Sample was weighed into a boiling flask into which 50% NaOH was added, followed by distillation of liberated ammonia, which was trapped in an excess of standard sulfuric acid solution. The resulting solution was back-titrated with standard sodium hydroxide. The boiling flask was heated with a burner, and after each analysis, extensive cleanup and reassembly of apparatus was required.

It was decided to buy an automated nitrogen distillation apparatus and a dead-stop titrator. The dead-stop titration vessel contained boric acid solution, which trapped liberated ammonia that could be titrated directly with standard acid solution to a set pH as the ammonia was distilled, using a time delay to sense the end of the distillation. Each sample took five minutes, and all reagents were dispensed by the nitrogen apparatus. The new setup was capable of processing 10 samples per hour, all with one piece of apparatus. Samples were weighed on a digital balance and transferred to the nitrogen still. The remainder of the analysis was done with the push of a button. All cleanouts were automated as the nitrogen unit and dead-stop titrator were both equipped with flow-through glassware. The nitrogen distillation equipment and an analytical balance were placed across from each other so that an analyst could handle all nitrogen determinations without moving out of a 15 square foot area. Safety was also markedly improved.

Manual titrations were eliminated by 90 percent after buying a stand-alone, dead-stop titrator for acid-base titrations. This titrator was physically placed next to the nitrogen distillation unit. This arrangement allowed all samples that supported a major product line to be done in three (3) hours instead of eight (8), thereby making an additional five (5) hours of labor available for other work.

A more sophisticated recording potentiometric titrator was purchased to handle argenometric and non-aqueous titrations. This unit could automatically determine endpoint and calculate results. The analyst needed only to enter sample weight and normality of the titrant. Titrants were contained in snap-in modules and were easily interchanged. Use of special electrodes, such as a combination silver electrode, allowed for direct titration of halogens with silver nitrate in solutions acidified with nitric acid, whereas this type of analysis would previously have required back-titration with thiocyanate ion after addition of excess silver ion (Volhard method). Analysts had only to weigh the sample, transfer it to a titration vessel, snap-in the appropriate titrant module, and proceed to titrate. Karl Fisher titrations were converted from manual to amperometric, thereby eliminating endpoint guesswork. Manual polarimetry was eliminated by acquisition of an automated, flow-though polarimeter with digital readout of angular rotation. This lab did about 5000 specific rotation determinations per year; thus, a substantial improvement in both efficiency and accuracy and savings in labor were realized.

All of these changes in the wet lab resulted in a doubling of efficiency for wet chemical analysis. In addition, most subjective measurements were eliminated, resulting in greater accuracy and improved lab credibility. The only techniques required from analysts were weighing, quantitative transfer, dilution, and aliquoting. The rest was automated.

The chromatography lab had four gas chromatographs and a data system that served all four GCs. Sample flow into this lab was continuous and random, consisting of distillation fractions and finished products from a variety of process areas, plus raw materials. Samples were injected manually, and columns were changed frequently to accommodate samples requiring different methods.

The first idea was to use autosamplers as a means of eliminating manual injections and freeing up some labor. However, efficient use of autosamplers requires a large number of the same kinds of samples to be injected consecutively using the same column and analytical method. This lab received its samples on a random but regular basis, and results needed to be turned in within an hour or less, usually within 30 minutes. With this type of workload, it was decided not to go with autosamplers, but rather, to develop a different approach for improving efficiency. It was observed that, as samples were submitted to the chromatography lab for GC analysis, they were run on whatever instrument was available. This involved changing columns and instrument conditions many times per day, resulting in delays and risk of cross-contamination. In addition, there were too many methods serving the mix of samples coming into the laboratory.

All the older GCs were replaced by state-of-the-art units. Since there were four gas chromatographs, it was clear that the great majority of samples needed to be run using a minimum number of methods. Methods were modified so that all samples could be run on four types of columns. GC#1 was fitted with Porapak™-Q, GC#2 with potassium hydroxide-treated Carbowax™ 20M, GC#3 with 10 percent SE-30 and GC#4 with 20 percent SE-30.

All samples could be run on one of these four GC columns with only minor changes to oven temperatures. Injection and detector temperatures were kept constant, and separate syringes were reserved for each instrument to avoid cross-contamination between different product types. These changes allowed for efficient operation of GC support to the plant with a minimum of delays.

Training of analysts focused on cookbook operation of instruments and on proper manual injection technique and syringe cleaning. All repairs and troubleshooting were done by supervision. The next step was to bring HPLC technology into the laboratory in order to reduce the amount of wet chemical testing.

Two major product lines had strong potential for HPLC analysis. One involved analysis of a reaction mother liquor to determine the amount of reconstitution necessary for proper stoichiometry in the next reaction. Wet analysis was cumbersome and non-specific. As the mother liquor got older with each re-use, impurities and breakdown products developed that could not be discriminated by titration. HPLC analysis led to baseline separation of all pertinent moieties and proper quantitation of analytes, resulting in better production yields and labor savings in the lab.

The other product line suffered from a similar problem in that reaction by-products could not be detected by wet methods. HPLC analysis resulted in an increase in plant yields from 88 percent to 99 percent. In addition, a major chunk of wet chemistry was eliminated.

While technology upgrades and rearrangement of wet lab geography was in process, the workload distribution, sampling, and scheduling was addressed.

Samples were delivered to the lab rather than analysts going to the plant to pick them up. Instead of one four-ounce bottle of each sample, the volume was reduced to one ounce, which was more than enough for complete testing and reduced cleanup and disposal time. Samples were delivered to the wet lab or the chromatography lab, depending on the testing required. However, plant personnel delivering samples were required to sign them in at a central location for ease of workload management in the lab. Where wet chemistry *and* chromatography were required, two samples were delivered–one to the wet lab and one to the chromatography lab. Commuting between laboratories for the purpose of sharing samples was eliminated.

Self-contained paperwork was used to minimize document control. Documentation, i.e., actual written methods, were contained in nine volumes of looseleaf binders. Each sample was written up so that each method was repeated each time. For example, if 50 samples required moisture, the moisture procedure was included in its entirety as part of each of the 50 individual monographs. Documentation was consolidated into one volume by writing each general procedure just once and then including only a reference to the general procedure in each individual monograph. Self-contained worksheets, such as those shown in Figure 4.1, plus use of procedures contained in a single methods book, resulted in gross simplification of documentation and reduction of clerical errors and mistakes resulting from usage of cumbersome documentation.

Assignments were made in parallel as much as possible. Analysts worked on either chromatography, general tests, nitrogen assays, or amino acid based testing. Data were checked by a senior analyst whose task it was to assign much of the work, to provide guidance to other analysts, and to communicate with the plant. The lab supervisor only had to deal with the senior analysts.

Workload matching was achieved by using rotating shifts. This was necessary since the unionized analysts would not volunteer the overtime needed to support 24-hour plant operations. One-third of

the analysts were assigned to work Monday through Friday, one-third Tuesday through Saturday, and one-third Sunday through Thursday. Each group had five regularly scheduled workdays. The result was full coverage, maximum utilization of lab equipment, near elimination of overtime, and no more Monday morning backlogs. Also, plant operations ran more smoothly and with fewer rejected batches, since lab results were available seven days per week on a demand basis.

In the environmental lab, plant environmental operators were trained to do the analyses necessary for wastewater control, giving the QC analysts more time for plant support. In addition, the environmental operators and QC analysts were cross-trained in essential elements of each others' jobs as a backup for sick and vacation days.

The improvement program needed to straighten out the lab described above was a continuous process that evolved over a five-year period. The problems were enormous and had to be solved in an orderly, progressive fashion. The end result was a lab that was efficient, credible, well-trained, and state of the art. But this is not the way to do things. It is far more desirable to design the lab operation to be well run from day one.

6.1.3 Planning It Right the First Time

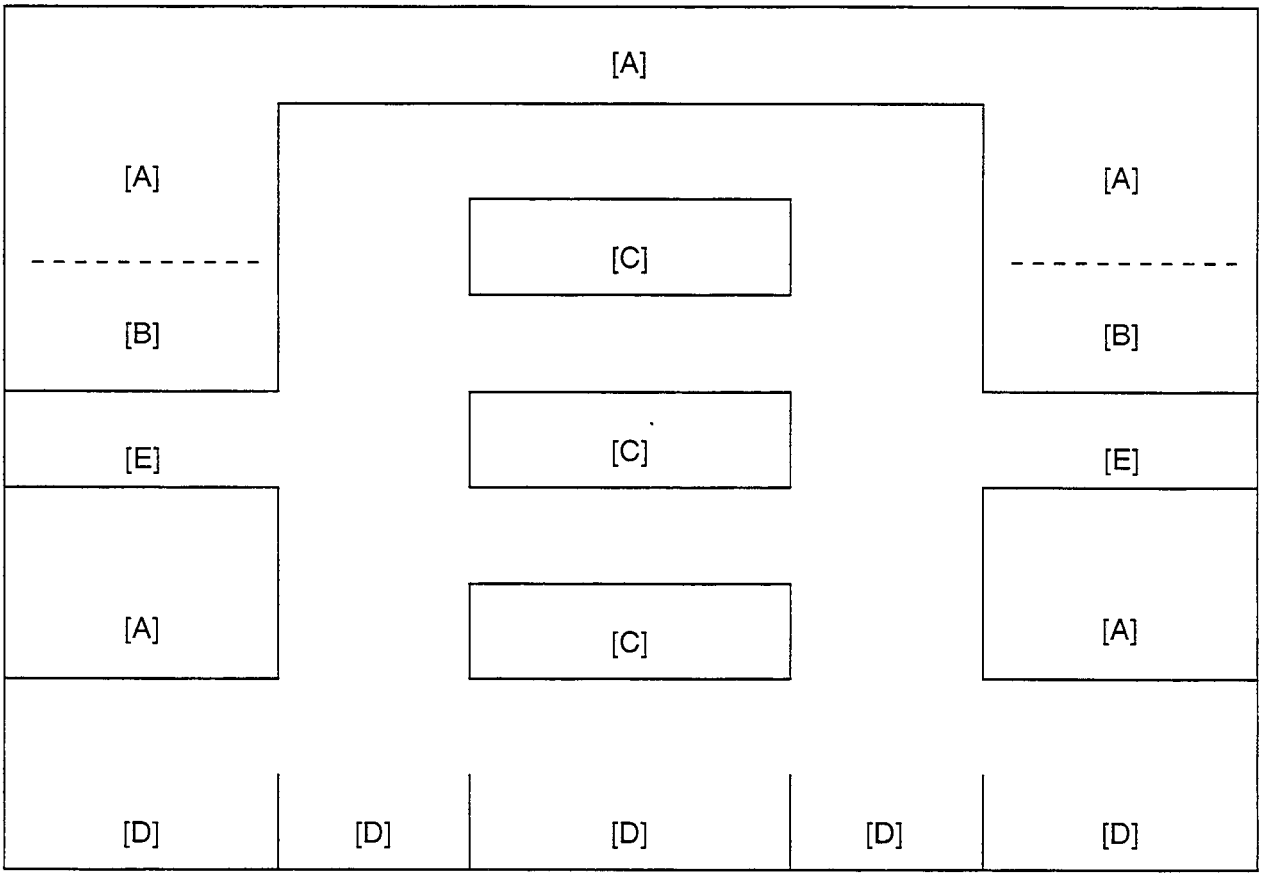
Figures 6.2 and 6.3 are two layouts better suited to efficient lab operations. Figure 6.2 is ideal for a high-volume QC or production support lab, while Figure 6.3 might be a more desirable arrangement for R&D or process development.

The type of open layout in Figure 6.2 is excellent from several standpoints. Shared equipment can be centrally located, samples are readily available to all, communications involving workload status are just a yell away, and supervision can be located in the area, which facilitates being on top of things. In addition, no one needs to walk very far to accomplish any given task.

The layout shown in Figure 6.3 allows for a think tank environment that includes a central area for sharing instrumentation (instrument room). Individual experiments or specialized work are done in individual labs. For R&D or process development, this can be desirable, because samples are specialized and must handled as such. Yet the open, shared area is still maintained to some extent with the centralized instrument room. Thus, research chemists maintain individuality and a quite place to think, while having many of the advantages of the wide-open, QC-type arrangement.

Many R&D chemists prefer the layout shown in Figure 6.3, but there is no reason why the lab in Figure 6.2 could not be used for R&D. For analytical R&D groups, this works quite well. Regardless of the laboratory arrangement used, the criteria of well-organized space, centralized equipment, minimization of motion by analysts, and a choice of lab equipment that best fits the workload is essential to efficient laboratory performance.

Figure 6.2. Example of an efficient layout for a high-volume QC or production support lab.



[A] = Analytical Instrumentation

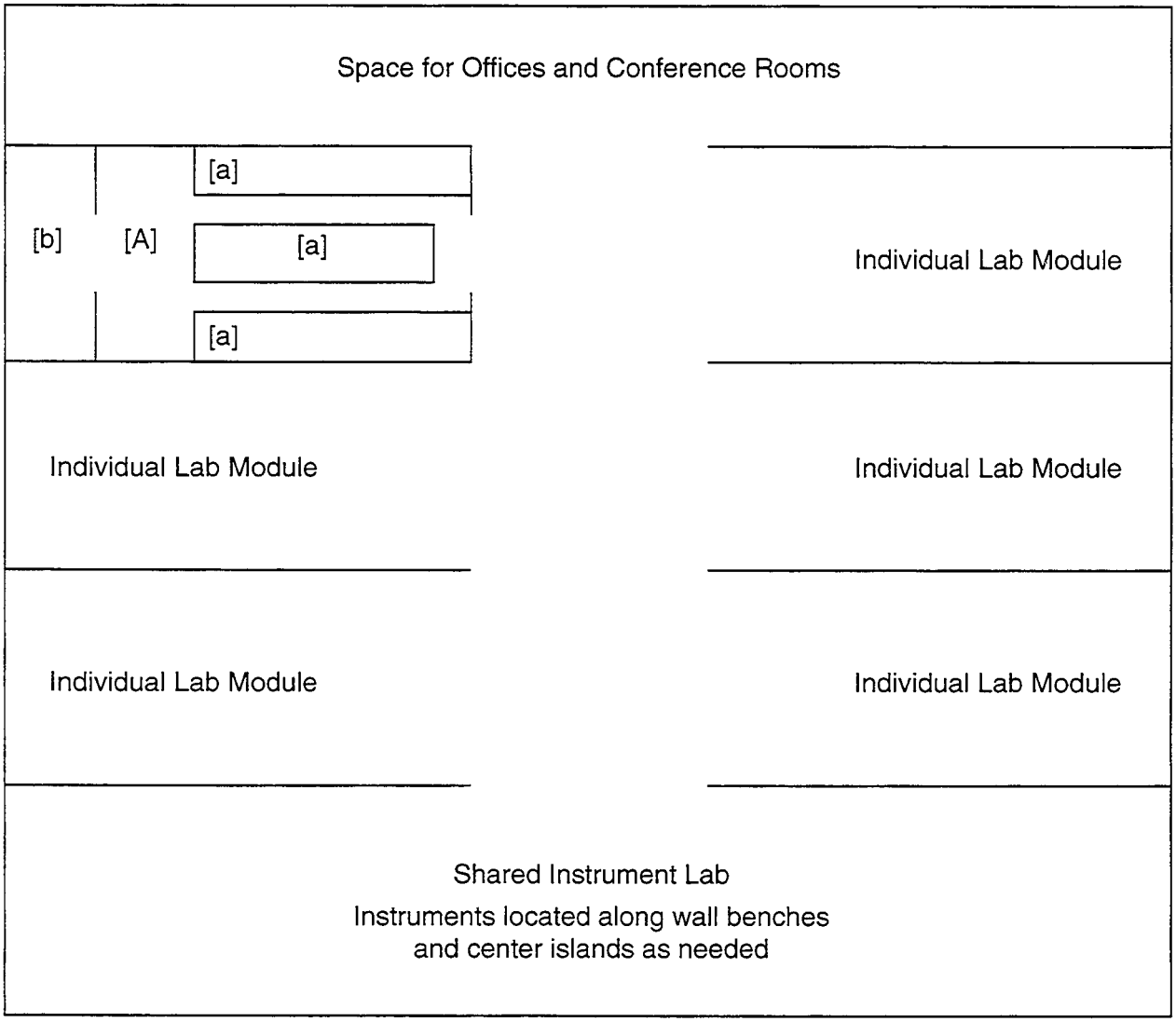
[B] = Fume Hoods

[C] = Center Islands for Sample Prep and Wet Chemistry

[D] = Office and Desk Areas

[E] = Analytical Balance Locations

Figure 6.3. Example of an efficient layout for an R&D or process development lab.



[A] = Typical layout for individual lab module, designed for one or two analysts.

[a] = bench space

[b] = desk space

CHAPTER

7

Tools of the Trade: Quality Assurance

7.1 QUALITY ASSURANCE FOR THE LABORATORY

What is quality assurance? There are probably as many theories and definitions as there are QC/QA managers, and a lot depends on which quality expert one is listening to. For the purposes of this book, assume that quality assurance is "The actions taken to assure that a finished product or service will perform as intended." In the analytical laboratory, the finished product is reported analytical data. Therefore, in the analytical laboratory, quality assurance is the standard operating procedures and actions that guarantee the efficacy of each and every analytical result.

It isn't enough to have chemists and technicians just doing analyses and handing in results. There are many activities in support of those analyses that must be performed on a regular basis to assure the quality of all the analytical data that are generated. These support activities are the actual components of an analytical laboratory's quality assurance program. Depending upon which industry one is looking at, there will be differences in quality assurance requirements as specified by federal or state regulations; however, "good laboratory practices are good laboratory practices," and this author will strive here to present comprehensive guidelines that will work for any analytical laboratory.

These guidelines consist of the following subsections:

1. Equipment Calibration and Maintenance
2. Standards and Reagents
3. Analytical Methodology
4. Documentation
5. Control Schedules
6. Retention Samples
7. Reporting and Treatment of Data
8. Statistical Quality Control

7.1.1 Equipment Calibration & Maintenance

A sound program of regular equipment calibration and maintenance is of paramount importance, and in fact, is the foundation upon which all analytical data are built or developed.

Consider a situation where a result is out of specification, questionable, or so far off target that it is clearly unreasonable. Where does one look to find out what happened? Investigation of suspect data depends upon knowing the condition and operational status of all laboratory equipment used in developing the data in question. Without knowing about the equipment, another unknown is introduced that can make interpretation of bad data either difficult or meaningless. A structured program of regular, ongoing calibration and maintenance of laboratory equipment is both smart and essential.

7.1.1.1 Analytical Balances

The analytical balance is the heart of almost every quantitative chemical analysis. Most laboratories have their balances serviced by an outside service engineer once or twice a year. The service call consists of cleaning, calibration, and documentation that the balance was serviced. The documentation is a sticker that the service engineer puts inside the balance chamber, certifying that he or she did the servicing on that particular date.

Suppose an analytical balance is serviced on January 1 and June 1 of each year. Suddenly, one day in April, a number of questionable results are generated. The balance is suspect, and an emergency service call is arranged. The service engineer finds the balance to be out of calibration and corrects the problem. The samples with questionable results are repeated and everything seems to be fine, or is it? What about samples that were run yesterday or last week or even on January 2? Are those results reliable? The answer is that you don't know for sure. Since the last calibration was January 1 and the balance was found to be out of calibration in April, all weighings made between January 1 and the time of the emergency service call in April are suspect. Why? because no one knows when the balance went out of calibration. Was it sudden or gradual? Again, no one knows for sure.

When dealing with laboratory equipment whose reliability is critical to the performance of the laboratory, that equipment must be checked *every day*. In the case of a balance, if the weight is wrong, so is everything that follows.

It is recommended that each analytical balance in the laboratory be serviced by a professional outside service engineer at least semiannually. High volume labs might consider quarterly service. In addition, the laboratory should check its analytical balances every day with standard balance weights. The weights used should be, at minimum, ANSI/ASTM Class 1 weights. These weights should be certified and supplied with a certificate of calibration. At the beginning of each workday, the balance should be checked with the standard, certified weights, using a series of weights that bracket the expected range of weighings for which the balance will be used. The calibration weighings should be recorded in a hardbound notebook that is reserved for balance calibration and maintenance.

If a balance is found to out of calibration on any particular day, only weighings made in the past 24 hours are suspect. The balance can be taken out of service and be recalibrated by a professional service engineer. The process of removing the balance from service, the service call, and reinstitution of balance use should be documented in the balance notebook. In addition to the chronology of events, a reason for actions taken needs to be recorded in the balance notebook. Certified weights

can be purchased from almost any scientific supply house, such as Fisher Scientific, VWR, or Thomas Scientific. It is recommended that two sets be purchased six months apart, because certified weights must themselves be recertified once a year, and while one set is out, balances still need to be checked on a daily basis. This daily check takes about 10 minutes and is well worth the time.

7.1.1.2 pH Meters

Another piece of laboratory equipment that is used rather heavily is the pH meter. Modern pH meters are supplied with manufacturer's instructions for calibration and use. These instructions should be followed as written.

In general, pH meters should be calibrated with known buffer solutions. These buffer solutions can be purchased ready made or can be prepared using buffer recipes found in publications such as the *United States Pharmacopeia* (USP) or the *Merck Index*. A calibration notebook should be kept near the pH meter. pH meters are used to make measurements over a wide pH range. For calibration purposes, one needs to know whether the expected pH of a sample is less than 7.0 or greater than 7.0. If the pH is greater than 7.0, the meter is calibrated with pH 7 buffer and another buffer of higher pH, usually pH 10. For measurements below 7, buffers of pH 7 and 4 are usually selected. The reason for this dual calibration is that pH meter amplifiers are perfectly linear, but electrodes are not. The meter is set to pH 7.0 with the 7 buffer using the CALIBRATE knob and with the SLOPE control set to 100 percent. The SLOPE control is used to set the pH meter to 4.0 or 10.0, depending on the calibration. This procedure matches the non-linearity of an electrode to the linear pH meter amplifier. The meter should be recalibrated before each and every use and the results of that calibration recorded in the pH meter calibration book. Entries made in the calibration book should include date and time, buffer lot number and expiration date plus the percent slope required to adjust the meter.

If the meter cannot be sloped, i.e., the value of the buffer cannot be dialed in with the SLOPE control, it indicates a problem with either the meter, the buffer, or the electrode. At this point, the meter is taken out of service and corrective action, such as using fresh buffer or reconditioning or replacing the electrode, must be taken. The corrective action sequence and reasons why must be documented in the pH meter notebook. Calibration of the pH meter before each use is necessary. However, the number of calibrations can be minimized by working in parallel and running groups of measurements at a time.

7.1.1.3 Spectrophotometers

UV/VIS and IR spectrophotometers are both used to varying degrees for chemical analysis. UV/VIS instruments are used for both quantitative and qualitative work. UV/VIS instruments can be wavelength calibrated with NIST traceable holmium oxide filters, which are commercially available from instrument manufacturers. Professional service should occur on an annual basis. In-house checks with holmium oxide can be done at some suitable interval, perhaps quarterly. The service and calibration record should be recorded in a log book dedicated to UV/VIS spectrophotometers. If the instrument is taken out of service, corrective actions and reasons must also be documented.

For quantitative UV/VIS analyses, standards, the values of which bracket the expected value of the sample, should be run with each analysis. The results of these standards are used to confirm linearity, extinction coefficient, and sensitivity. For qualitative work, the absorbance minima and maxima at certain wavelengths are compared for a sample versus a standard as a means of confirming identity. Any values for the standards that deviate from what is expected must be investigated,

corrected, explained, and documented. The expected values are those defined in each lab's SOP, which should include acceptable ranges for standard parameters. Following these procedures will insure that problems such as weighing, sample transfer errors, or instrument problems are quickly identified. In the case of IR spectrophotometers, when used for quantitative work, the same rules apply as those for UV/VIS units. Infrared spectrophotometers are wavelength calibrated using a thin film of polystyrene.

7.1.1.4 Chromatography Systems

Chromatographic systems, specifically gas chromatography (GC) and High Performance Liquid Chromatography (HPLC) systems, are among the most widely used tools in today's analytical laboratory. These systems are very powerful analytical tools because of their speed and specificity. But they are also complex systems consisting of many parts. Unlike a balance or pH meter, a chromatographic system is actually a combination of several instruments connected together to form an analytical system.

A gas chromatograph is made up of an injector, column oven, detector, and in many cases, an autosampler. The HPLC system is made up of discrete autosamplers, pumps, and detectors, which are connected together to form complete HPLC systems. How then is the task of calibration and maintenance for these multicomponent systems done?

Rather than deal with each component as a discrete instrument, it makes more sense to treat the entire system as a single entity and to use calibration or checking techniques that define proper operation of that single system. This is accomplished in one of two ways.

The first is to maintain a checklist of instrument conditions that must be checked at the beginning of each day. For gas chromatography this will include checking gas cylinders, changing injector septums, setting instrument parameters to settings specified in the method monograph, and balancing the detector amplifier output to zero once a steady baseline has been achieved. These items should be documented each day to show that they were done. For HPLC systems, this will include making sure that there is sufficient mobile phase; setting the instrument parameters to settings specified in the method monograph, such as flowrate and detector wavelength; and balancing the detector amplifier to zero once a steady baseline has been achieved. Once the physical checklist is done, it is time to measure system performance criteria to assure that the entire system is operating as expected.

For gas chromatographs, a standard mixture should be injected prior to the beginning of an analytical run. There needs to be a standard mixture for each different sample mixture. If the retention times, relative retention times and response factors for the components of the mixture fall within acceptable limits, as defined by the applicable SOP, then the system is ready for analytical work. If there is a deviation from accepted values, a new standard mix should be prepared, and if the deviations still exist, then diagnostic troubleshooting on the system is in order. Daily checkout, downtime, solutions to problems, and explanations of deviations all need to be documented.

For HPLC systems, the best performance test is "system suitability" as defined in the USP. System suitability is established by measuring the relative standard deviation among the results of five or more standard injections done at the beginning of the chromatographic run. The relative standard deviation in most cases should be 2.0 percent or less. In addition, performance parameters, such as tailing factor, resolution factor, capacity factor (K'), and response factors, need to be determined. If all four parameters (relative standard deviation, tailing factor, resolution factor and response fac-

tors) are within limits specified in the applicable SOP, then the entire system is deemed acceptable and suitable for sample analysis. If any deviations are observed, a fully documented investigation, with corrective action, must be performed before resuming sample analysis.

System suitability can be applied to gas chromatographs as well, but it isn't as critical, because GC columns are far more durable and consistent than HPLC columns. As long as retention times and response factors are within acceptable limits, the system will function as expected. System suitability testing for GCs is somewhat like chicken soup; it might not help, but it can't hurt; and in the pharmaceutical industry, for example, it is a regulatory requirement. The important thing is that retention times, detector response, reproducibility, and peak shapes are consistent and conform to a specified standard. This defines injector reproducibility, column performance, and detector response for an integrated analytical system.

In addition to the physical and performance checks described above, which are done prior to analysis of sample, it is necessary to monitor that performance throughout the entire analytical run. This is accomplished by injecting standards periodically, every five or six samples for instance and at the end of the run, and checking these performance criteria each time that a standard is injected. If standards fail to meet established criteria, the system must be diagnosed and corrected, and all samples injected after the last "good standard" must be reinjected. Only samples that are bracketed by good standards can be accepted as valid.

7.1.1.5 Integrators and Data Systems

There is ever increasing pressure to validate electronic integrators as a means of proving that they are reliable. It is recommended that integrators be validated on a one-time basis and that the validation be documented in a formal validation report. There are two parts to integrator/data system validation: accuracy of the electronics in performing integrations of peak signals and accuracy in doing analytical calculations based on those integrations. Integrator validation is best accomplished by use of a calibrated input source, such as an electronic peak/signal generator. Such a unit, which is calibrated and NIST traceable, is available from several sources.

The validation scheme should start by demonstrating that the output of each integrator is accurate. This is accomplished by inputting a calibrated signal into an integrator and showing that the area unit output corresponds to the microvolts per area unit specified by the manufacturer of the integrator. Once the electronics have been validated in this manner, a standard and sample chromatogram should be used to calculate an assay result manually. Then compare the result with that generated by the integrator/data system. By combining the electronics verification with a manual assay calculation, validation of both the integrator and the data system is achieved.

It is recommended that several sets of data be employed and that all calculation types normally used on a particular data system, such as internal standard and external standard, be subjected to a manual versus integrator calculation result comparison.

7.1.1.6 Atomic Absorption Spectrometers

Another commonly used laboratory technique is atomic absorption (AA), which is primarily used for macro or micro quantitative analysis of inorganic cations. A typical example is determination of milliequivalents of potassium in potassium chloride tablets. Atomic absorption units are basically UV/VIS spectrophotometers whose sample "cell" is a flame and whose source is a hollow cathode lamp that emits atomic lines specific to one or more elements. This example deals with Flame AA.

AA units can be treated in a manner similar to UV/VIS units in terms of calibration, but the check-out procedure is somewhat different. Before use, gas supplies must be checked. Acetylene tanks must never be allowed to drop below 75 PSI to avoid contamination of the instrument gas box with acetone, which is a solvent for commercial acetylene. Also, nebulizers, tubing, and burner heads need to be checked to be sure that they are in good condition. The instrument is then set up as per manufacturer's operating instructions and analytical parameters are set as called for in the analytical monograph.

The value of each sample is determined by comparison to a standard curve, prepared from fresh standards, whose upper and lower values bracket the expected value of samples that are to be run. One standard should be interspersed approximately every five samples and at the end of the run. This procedure verifies linearity and stability of the standard curve (slope) during the analytical run. As with other calibrations, all setup and verification with standards needs to be documented.

Graphite furnaces, hydride generators, and inductively coupled plasma (ICP) units are somewhat different. They differ from flame units in sensitivity and/or ability to control interferences. However, the concepts of establishing linearity throughout the analytical working range and slope stability still apply.

7.1.1.7 Miscellaneous Equipment

Karl Fisher apparatus used for water determinations, ovens, refrigerators, incubators, muffle furnaces and water baths, or any other controlled temperature device or area should have a log book in which daily temperature readings are entered. In some cases, such as controlled-temperature storage areas used for stability sample storage, it is important to have a 24-hour recording chart that measures temperature continuously.

Thermometers used to measure *any* temperature must be calibrated periodically against NIST traceable thermometers in order to assure their reliability and accuracy. Calibrations must be documented. Certified, NIST traceable thermometers can be obtained from any scientific supply house. As with certified weights, thermometers need to be periodically recertified.

Top-loading balances, used for rough weighings, should have outside servicing at the same frequency as analytical balances. However, since these are used for general weighing, it is not necessary to do daily checks with certified weights. Instead, weekly checks with larger weights can be performed, using NIST (NBS) Class P weights, which can be obtained individually and are available in denominations of up to 30 Kg.

There are other pieces of apparatus that might be used in an analytical laboratory in addition to the more common ones just described. These include polarimeters and sample preparation devices, such as extractors and head-space units. Whatever the case, some traceable standard or performance parameters must be utilized to assure accuracy and reliability.

7.1.1.8 Standards

Another critically important foundation for all analytical work is the integrity of the standards used. For spectroscopy and chromatography, a primary standard of known, certified purity must be used as the reference against which all samples are measured. Such standards can usually be purchased

from commercial sources, such as the United States Pharmacopeial Convention or scientific supply houses that specialize in high purity chemicals, suitable for use as primary standards. When such standards are purchased, they must be logged in by recording the date received, lot number, purity, and expiration date (if any). This information should be kept in a standards logbook.

The standards, when not in use, must be stored under conditions specified by the supplier or by the analytical monograph. This could be room temperature, desiccated, refrigerated, or even frozen. The USP, for example, specifies storage conditions for each standard that it sells. Access to standards should be restricted to supervisors, who will issue standards to analysts as needed. When the analyst is finished, the standard must be returned to storage. The issuing and return of standards to storage must also be documented.

Primary standards are expensive and can cause a financial strain on many laboratories. In order to control costs, these laboratories will often use small weighings when using standards (10 or 20 milligrams) that can, and will, compromise accuracy. For frequently run analyses, it is better to use a house standard. A house standard can be prepared by checking the purity of an in-house lot of sample with the primary standard. The purity check should be repeated several times, until acceptable reproducibility is obtained on at least three separate assays in which separate weighings of primary standard and prospective house standard for each assay have been used.

One way to determine acceptable reproducibility is to set a maximum percent relative standard deviation limit on the results of the three house material assays. Once the purity of the house material has been determined with certainty, it can be used as an analytical standard. As with the primary standard, all work must be documented, particularly the raw data relating to the certification of the house material as an analytical standard. Special care must be taken to record expiration and recertification dates so that the house standard will not be used beyond its expiration. For titration work, commercially available titrimetric primary standards are both pure and cost effective.

7.1.1.9 Reagents

All chemicals purchased by the laboratory should be logged in and the date of receipt, lot number, and expiration date recorded. It is extremely important that a routine inspection of reagent logs be done (monthly) to make sure that out-of-date reagents are removed from the laboratory and discarded. This also applies to test solutions, purchased buffer solutions, and other prepared solutions. Each should be labeled with a date of preparation (or date of receipt) and an expiration date. In addition, for reagents prepared in the laboratory, a notebook reference to the preparation should be part of the documentation.

7.1.1.10 Volumetric Solutions

The preparation and standardization of volumetric solutions also needs to be thoroughly documented. The items that need to be recorded are the lot number and expiration date of the materials used to prepare the solution, the lot number and expiration date of the primary standard used to perform the standardization, and the raw data for the standardization, including weights, titers, calculations, and results. Standardizations should be performed in triplicate with a precision of 0.05 percent or better. The final volumetric solution needs to be properly stored and affixed with a label that states the name of the solution, the exact normality, date of standardization, expiration date, and notebook reference to raw data on preparation and standardization.

As with any other reagent, expiration date checking should be done regularly. In the case of volumetric solutions, if a significant amount of solution remains after the expiration date, the solution can usually be restandardized. Thus, the expiration date of volumetric solutions is often referred to as the restandardization date. Note: Even store-bought standardized solutions must still be standardized in-house.

7.1.1.11 Water

Distilled or deionized water used for analytical work must be pure. Most laboratory water systems use in-line conductivity meters to measure the resistance of the purified water put out by the system. The reading should be recorded daily. Also record any deviation or corrective action taken to remedy an out-of-spec condition. Proper resistance levels for any laboratory's water need to be defined in that laboratory's SOP for purified water systems. The USP provides guidance for the quality of laboratory water.

7.1.1.12 Dissolution Apparatus

One of the principal and most important pieces of equipment in today's pharmaceutical laboratory is the dissolution equipment. There are currently two dissolution apparatuses listed in USP 23 under "Dissolution" <711> and seven apparatuses listed under "Drug Release" <724>, covering a wide variety of pharmaceutical dosage forms such as tablets, capsules, topicals, and time-release products.

The reader is strongly encouraged to read the USP carefully in reference to drug release techniques and to be especially attentive to maintenance, usage, and calibration of each dissolution apparatus in the laboratory. Dissolution is an FDA "hot button," and should not be treated lightly. An SOP for calibration and use of dissolution equipment is attached to this chapter.

7.1.1.13 General Comments

The procedures just discussed for various instruments and apparatus are given as minimum, but stringent, components of quality assurance for the analytical laboratory. These techniques are the operational part of laboratory quality assurance and must be combined with appropriate documentation and training.

Before continuing, there are some general considerations that need to be mentioned with regard to overall laboratory quality assurance as it applies to instrument calibration and maintenance. In any analytical scheme where large numbers of samples are to be run, it is recommended that a standard be run at the beginning of the run, after each fifth sample, and at the end. Criteria for evaluation of this scheme are discussed under calibration and maintenance of chromatographic systems.

Parts replacements or changes to an instrument, such as replacing lamps, columns, detector parts, pump seals, or any other change, should be documented in the logbook associated with the particular instrument. After any such maintenance or service is performed, equipment should be recalibrated in order to ensure proper performance.

Instrument systems such as GC or HPLC should be labeled as System #1, System #2, etc. so that reference to any instrument can be made by system number. System number should be referenced in calibration, repair, and the performance of analytical work. In addition, a master log should be kept that describes for each system, its components, serial number of each component, and the location (room number) of the system.

It is not necessary to have a hardbound notebook for each and every individual instrument, but rather a hardbound notebook for each group of instruments. For example, if a laboratory has five HPLCs, two pH meters, and three UV spectrophotometers, it would not need 10 calibration and maintenance log books, but rather three books: one for HPLCs, one for pH meters, and one for UV spectrophotometers. By referencing system numbers, it is always clear as to which system has been calibrated or serviced.

The key to a solid calibration and maintenance program for laboratory equipment is having specific SOPs and documentation for checking out equipment before use; monitoring it during use; and if any deviations occur, taking the unit out of service until proper operation is restored and verified. The need to document all calibration and repair actions cannot be overemphasized.

There are many pieces of apparatus and some instruments that were not included in this discussion such as GC-MS (gas chromatograph-mass spectrometer) and NMR (nuclear magnetic resonance spectrometer). For this work, it was decided to present a picture of quality assurance requirements for instruments most commonly used by analytical laboratories.

In the chapters that follow, the concept of control samples and how they can be used to achieve outstanding and cost-effective quality assurance for the analytical laboratory will be explored.

7.1.2 Analytical Methodology

What is the main component of quality assurance for analytical methods? The answer is validation. A well-written analytical method is one where the average chemist or analyst can do the analysis by reading the method, with no further instruction or input. It should list all equipment and reagents needed to perform the method, a detailed step-by-step procedure, and a detailed explanation of calculations and results units. In addition, if spectra or chromatograms are generated, a sample spectrum or chromatogram must be part of the method.

Having a thorough, well-written method is fine, but it still must be shown, by laboratory studies, that the method is suitable for its intended analytical application. That's where validation comes in. The degree and type of validation will vary depending upon the type of method. For simple UV methods, linearity and range may be adequate, while for HPLC assays of finished pharmaceuticals, for instance, validation requires selectivity, linearity, range, precision, accuracy and recovery, limit of detection, limit of quantitation, ruggedness, and robustness, and must be shown to be stability indicating. Stability indicating means that, when subjected to stress conditions, such as heat, light, acid and alkaline hydrolysis and oxidation, the sample breakdown products do not interfere with quantitation of the target analyte or analytes.

Regardless of the analytical method, it must include documented validation. Any changes in the method will result in the need to revalidate, either fully or partially, depending upon the nature of the change. Methods must be uniquely labeled. Each time a revision is issued, it must also be uniquely labeled. For example, if a method is issued as Method #100, its revisions might be labeled 100A, 100B, etc., adding the next higher suffix to each revision in order to identify it in a unique manner. The original issue and each subsequent revision should include the date of issue and have multiple approval signatures. Only copies of the most recent revision should be located in the working laboratory. Older revisions should be archived in a central, secure location for reference. A mechanism of document distribution should be established for handling new revisions. The recipient should sign

off that the new revision has been received and must return the copy of the previous revision along with a sign-off sheet, which can act as a receipt of distribution and prior revision recovery.

Each method should contain a History Section that lists, for each revision, the date of change and the reason for the revision. Similarly, validation reports should contain a history section to explain reasons for revalidation, as dictated by method changes.

7.1.3 Documentation

The importance of proper documentation in the analytical laboratory cannot be overemphasized. Laboratory documentation can be subdivided into five major types.

1. Standard Operating Procedures (SOPs)
2. Analytical Methods and Validations
3. Notebooks (or Worksheets)
4. Specifications and Report Sheets
5. Calibration and Maintenance Logs

7.1.3.1 Standard Operating Procedures

Standard operating procedures (SOPs) are the "how to do it" documents for the laboratory. There should be an SOP for each and every operation and procedure that is performed in the laboratory. Every task and procedure, such as calibrations, maintenance, safety procedures, and specific analytical procedures, must have SOPs. Some sample topics for analytical laboratory SOPs include

- Analytical methods validation
- Calibration of analytical balances
- Calibration of GC systems
- Calibration of HPLC systems
- Calibration of pH meters
- Calibration of UV/VIS spectrophotometers
- Calibration of thermometers
- Chromatography analysis
- Determination of extinction coefficient
- Dissolution testing
- Laboratory notebooks
- Laboratory safety procedures
- Laboratory sample flow
- Management of analytical methods

- Management of analytical standards
- Management of specification sheets
- Material Safety Data Sheets (MSDSs)
- New employee training
- Retention samples
- Sample retesting intervals
- Standardization of volumetric solutions
- Treatment of data

This list is just a partial sampling of typical SOP topics. Any particular analytical laboratory will probably have most of these plus many more. The point is that *every* operation and procedure must be covered by a written Standard Operating Procedure.

As discussed in chapter 2, SOPs should be structured so that they contain several key sections. "Purpose" defines the purpose or objective of the SOP, such as calibration of analytical balances. Next is "Scope," which lists the personnel within the organization who are covered by, or have responsibility for, the activity stated in the Purpose section of the SOP. Scope usually lists departments, such as Quality Control, R&D, or Manufacturing. SOPs may also refer to specific individuals by title, such as Laboratory Supervisors or Director of Quality Control. The Purpose and Scope sections are followed by the Procedure section, which lists the specific steps (cookbook) for performing the intended purpose of the SOP.

An SOP should be specific enough for the intended purpose to be carried out consistently by any laboratory worker to whom the SOP applies, and should provide a list of instructions designed to minimize human error and variation between laboratory personnel (Storytelling Syndrome). Although an SOP needs to be specific, it should not be so detailed that it limits the laboratory so much that it cannot make responsible changes to the SOP. In fact, every SOP should include a "What If?" section that spells out procedures for dealing with deviations from expected results. For example, an SOP that lists the steps for daily checking of an analytical balance should also list what actions are to be taken if the balance is out of conformance.

Finally, every SOP must be signed by responsible members of management (more than one signature) after approval or modification, and training in the use of the SOP must be given to all personnel defined by the Scope of that SOP. An excellent summary of proper SOP requirements can be found in the United States Code of Federal Regulations, TITLE 21, Part 211, Subpart I–Section 211.160 and Subpart J–Section 211.194.

7.1.3.2 Analytical Methods and Validations

Analytical methods are SOPs that describe, in detail, procedures for performing actual analytical work. They are more detailed than regular SOPs and define, very specifically, all aspects of analyses. Analytical methods and their corresponding validations are discussed in Section 7.1.2, "Analytical Methodology."

7.1.3.3 Laboratory Notebooks (or Worksheets)

Laboratory notebooks are considered legal documents that, in some instances, can actually be brought into court as proof of whether or not a piece of work was actually done. As a rule, it is best to follow the same policy that FDA follows, which simply stated, is that "if something isn't written down, then it wasn't done." All analytical work must be documented and must show date, name of analyst, which analytical method or procedure was followed, raw data (weights, titers, instrument readings, spectra, and chromatograms), calculations, and results. In addition, all work must be initialed by the person doing the work and witnessed and countersigned by a supervisor or another technically qualified responsible person who must state by his or her signature that the work was witnessed and understood.

Work must be entered in chronological order, and any unused portions of a page must be blocked out. Finally, any errors are to be corrected by drawing a single line through the value that is incorrect, and then writing in the correct value above the one that was crossed out. The change must be initialed and dated, and unless the reason for the change is blatantly obvious, a short explanation of why the change was made needs to be written into the notebook, which must also be initialed and dated.

The above procedure provides an ironclad audit trail for analytical data. Notebook management should have its own SOP. Training on the use of that SOP for all analysts is strongly recommended.

Similarly, if worksheets are used (self-contained paperwork), the same rules of documentation apply. All work has to be shown, including correction of errors and explanations for any deviations from the norm. Restating our general policy of documentation, "If something isn't written down, then it wasn't done."

7.1.3.4 Specifications and Report Sheets

A specification sheet is a document that lists the specifications for a raw material, in-process material, or finished product. Similarly, a report sheet is a document upon which final analytical results for a particular sample are reported and signed off for submission to the laboratory's customer. They are best combined as a single document, such as the one shown in Figure 3.2.

These documents are subject to the same criteria that are applied to analytical methods. Only the most current revision is used in the working laboratory, with older revisions being centrally archived. In addition, revision numbering systems need to be clear, and a history should be maintained for the purpose of defining the reasons for change and revision.

7.1.3.5 Calibration and Maintenance Logs

All calibration, repairs, or changes to laboratory equipment and/or analytical systems must be recorded in an appropriate logbook. The logbook should be hardbound, with a book reserved for each class of instruments.

Entries should include date, what was done, and the signature and comments of the individual performing the work. The practices described in our discussion of notebooks applies here as well. Calibration and Maintenance Logs should be used, not only for routine calibration and repair, but also for recording work done as part of any preventative maintenance program that is included in laboratory SOPs. Preventative maintenance will be addressed as a productivity tool in subsequent chapters.

7.1.4 Control Schedules

What are control schedules? They are nothing more than a written reference to what tests or control procedures are required for a particular material. Generally, those tests are defined by specifications; however, there are many instances where additional testing is done beyond what is required by specifications. There are a variety of reasons for these additional requirements, such as production control or statistical programs to develop new criteria. In any event, there must be a definitive written document that defines the testing or control requirements for each material that is submitted to the laboratory. Some laboratories choose to have a separate document, which just means more paperwork. It makes more sense to have the control schedule built in as part of the specification/report sheet. This document, such as that shown in Figure 3.2, can include, not only specifications, but also non-specification tests. In the specification column, simply put "Report Only" as the specification. This statement says that the test is to be run, but its value is to be reported only, and has no bearing on sample disposition.

7.1.5 Retention Samples

Another important component of quality assurance for the analytical laboratory is the keeping of retention samples (reserve samples). As a general rule, a sample of every lot of material that is shipped, and the raw materials that went into those lots, should be retained for a period of at least one year beyond the expiration date of the shipped material. The quantity of retention samples should be at least twice the amount needed to perform all analytical testing required by the material's analytical monograph. In addition, retention samples should be stored in an appropriate secured area, taking into account sensitivity to environmental factors such as light, heat, and humidity. There should be an SOP that clearly defines the taking, labeling, and storage of retention samples.

The United States Code of Federal Regulations, Title 21, Part 211, subpart I, section 211.170 gives a detailed description of reserve sample requirements for pharmaceuticals, which may be applied to other industries as a general guideline.

7.1.6 Reporting and Treatment of Data

Reported data (analytical results) are like first impressions in that they are very difficult to take back or to change. Therefore, it is absolutely imperative that confidence in analytical results be very high and that this confidence is shared by both the laboratory and the customer.

Reliability of reported data is largely dependent upon the treatment of that data. In addition to the actions presented earlier in this chapter, such as equipment calibration, proper control of standards and reagents, sound documentation, and use of reserve samples, it is also necessary to have final checking procedures to assure that the reported data are indisputable.

The last step in the analytical process is the audit process. Once an analyst writes down analytical results on a final report sheet and signs off on those results, the work must be independently audited. A second person, usually the supervisor or designated auditor, should check each result to make sure that it conforms to current specification requirements and should look at raw data and check calculations to be sure that all work has been done and that computations and transcriptions, if any, are correct. The auditor should also verify that the proper analytical methods and correct revisions were used. Once thoroughly audited and countersigned, the results can be submitted to

the customer. In the event a mistake is discovered, explanations with dates and initials must be documented prior to changing any results. "Bad" data must *always* be explained.

7.1.7 Statistical Quality Control

There are many mine fields in the analytical laboratory, which can upset the best laid plans of any laboratory manager or supervisor. Variables such as people, instrument performance, and environmental factors can all provide opportunities for problems and errors to occur.

In addition to the quality assurance techniques already discussed, we need to utilize statistical quality control (SQC) as a quality assurance tool for the laboratory. Statistical quality control allows the laboratory manager to monitor both internal and external performance in an unbiased fashion. It provides laboratory credibility second to none and is an invaluable tool for signaling changes in laboratory performance parameters, or manufacturing plant performance. at an early stage, before an out-of-control condition develops.

This chapter has dealt, in detail, with techniques and requirements for laboratory quality assurance. In the case of SQC, detailed discussion, and use of actual examples, will occur in chapter 9.

7.2 AUDITING

After all QC/QA systems are in place for the laboratory, the best way to check systems for integrity, and to maintain that integrity, is through the process of auditing. Whether the audit is internal or a laboratory certification audit done by an outside consultant, the audit process must be ongoing as a means for sustaining compliance, and as a means for achieving continuous self-improvement. Currently, FDA has been interested in laboratory certification, which should be done by an outside auditor who has the training, education, and experience to conduct such an audit. Part of this audit is the preparation of a certification manual that must be updated on a yearly basis and is heavily weighted towards training and maintenance of training records.

A basic Laboratory Compliance Manual is included at the end of this chapter to help laboratory managers develop a sensible and comprehensive audit plan for their own laboratories.

In addition to internal audits, each outside contract laboratory that does work for another laboratory should be audited once a year by the requisitioning laboratory.

With this in mind, a basic lab compliance document is included herein as a guideline for the reader.

REFERENCES

21 CFR 211, April 1993, Washington: Office of the Federal Register.

The Merck Index, 11th Edition, Rahway: Merck & Co., Inc.

USP 23/NF 18, Rockville: United States Pharmacopeial Convention, Inc.

STANDARD OPERATING PROCEDURES

CHAPTER 7: QUALITY ASSURANCE

SOP 007:	Equipment Maintenance and Calibration
SOP 008:	Calibration of Analytical Balances
SOP 009:	Calibration of Top-Loading Balances
SOP 010:	Calibration of pH Meters
SOP 011:	Calibration of UV/VIS Spectrophotometers
SOP 012:	Calibration of Infrared Spectrophotometers
SOP 013:	Calibration of High Pressure Liquid Chromatographs
SOP 014:	Validation of Integrators and Data Reduction Systems
SOP 015:	Calibration of Flame Atomic Absorption Systems
SOP 016:	Calibration of Ovens
SOP 017:	Calibration of Furnaces
SOP 018:	Calibration of Thermometers
SOP 019:	Calibration of Refrigerators
SOP 020:	Management of Analytical Standards
SOP 021:	Certification of House Standards
SOP 022:	Calibration of Karl Fisher Apparatus
SOP 023:	Handling of Test Solutions, Indicator Solutions, Buffer Solutions, Solvents, and Dry Chemicals
SOP 024:	Preparation and Standardization of Volumetric Solutions
SOP 025:	Instrument Operating Procedures
SOP 026:	Standard Practices for Chromatographic Analyses
SOP 027:	Sample Analytical Monograph (Single Test Style)
SOP 028:	Sample Analytical Monograph (Full Monograph Style)
SOP 029:	Analytical Methods Validation
SOP 030:	Laboratory Documentation Control and Distribution
SOP 031:	Calibration and Use of Dissolution Apparatus (Paddle or Basket)
SOP 032:	Auditing of Analytical Data
SOP 033:	Laboratory Failure Investigations
SOP 034:	Reserve Samples
SOP 035:	Raw Material Testing and Vendor Certification
SOP 036:	Equipment Identification
SOP 037:	Audit of Outside Laboratories and Internal Laboratory Audits

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Equipment Maintenance and Calibration**	NUMBER: **007**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide a schedule for laboratory instrument calibration and maintenance and to define required documentation for such calibration and maintenance.

2.0 SCOPE:

2.1 All laboratory apparatus used for analytical measurements.

3.0 RESPONSIBILITY:

3.1 Laboratory directors, managers, and supervisors.

4.0 FREQUENCY:

4.1 Per Procedure

5.0 PROCEDURE:

5.1 Laboratory Instrument In-house Calibration Schedule

5.1.1	HPLC systems:	Three (3) months
5.1.2	GC systems:	Six (6) months
5.1.3	UV/VIS Spectrophotometers:	Six (6) months
5.1.4	Infrared Spectrophotometers:	Monthly
5.1.5	pH Meters:	Each use
5.1.6	Analytical Balances:	Daily
5.1.7	Karl Fisher Apparatus:	Each use
5.1.8	Melting Point Apparatus:	Each use
5.1.9	Refractometer:	Each use
5.1.10	Top-Loading Balances:	Monthly

5.1.11	Flame Atomic Absorption:	Each use
5.1.12	Thermometers:	Yearly
5.1.13	Dissolution Apparatus:	Six (6) months

5.2 Maintenance/Calibration—Outside Contractor/Vendor Schedule

5.2.1	HPLC Systems:	Yearly
5.2.2	GC Systems:	Yearly
5.2.3	UV/VIS Spectrophotometers:	Yearly
5.2.4	Infrared Spectrophotometers:	Yearly
5.2.5	pH Meters:	When out of service
5.2.6	Analytical Balances:	Six (6) Months
5.2.7	Karl Fisher Apparatus:	When out of service
5.2.8	Melting Point Apparatus:	When out of service
5.2.9	Refractometer:	When out of service
5.2.10	Top-Loading Balances:	Six (6) months
5.2.11	Flame Atomic Absorption:	Six (6) months
5.2.12	Thermometers:	Yearly
5.2.13	Dissolution Apparatus:	When out of service
5.2.14	Calibration Weights:	Yearly
5.2.14	Oven and Furnaces:	Yearly
5.2.15	Refrigerators:	Yearly
5.2.16	Controlled Temperature and/or Humidity Chambers (Stability, etc):	Yearly

5.3 Documentation

5.3.1 All calibration and maintenance performed on laboratory equipment must be recorded in a laboratory equipment maintenance and calibration notebook. This includes both in-house and outside contractor/vendor service.

5.3.2 Separate books should be kept for each class of instruments, such as one for balances and one for HPLCs. In a case where there is more than one of a particular instrument, such as HPLCs, identify each instrument by a system or instrument number, such as HPLC #1, that identifies that particular equipment as the unit being calibrated or repaired.

5.3.3 Store all outside service reports as part of the calibration and maintenance records.

5.3.4 There must be individual SOPs in place for calibration and maintenance of all laboratory equipment.

5.3.5 To each instrument or apparatus that is calibrated or serviced, a sticker must be affixed to that piece of equipment, indicating the calibration date, calibrated by whom, and date when calibration expires. Stand alone units only need one sticker, while units composed of separate components such as HPLCs can have individual stickers on each component, or can have one sticker for a whole system consisting of specific components. In the latter case, a system ID must be recorded that defines each component associated with that system, including individual component serial numbers.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Analytical Balances**	NUMBER: **008**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To assure the accuracy of analytical laboratory balances.

2.0 SCOPE:

2.1 Analytical balance, electronic or electromechanical.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Daily

5.0 PROCEDURE:

5.1 Materials

5.1.1 NIST traceable weights, Class S or better, 10 mg–100 gm

5.2 Calibration Check

5.2.1 Check the accuracy of each analytical balance by weighing 10 mg, 50 mg, 100 mg, 1 gm, 2 gm, 5 gm, 10 gm, and 20 gm NIST-traceable weights. Make sure that the weights used bracket the weighings normally used for analytical work.

5.2.2 Record the actual weight values obtained for each of the standard weights.

5.2.3 The observed value should be within 0.1 percent of the individual values cited on the weight calibration certificate for each weight.

5.2.4 Record all weighings in an analytical balance calibration logbook.

5.2.5 If any weights are out of specification, take the balance out of service until it has been recalibrated and certified by a qualified balance service technician.

5.2.6 Have regularly scheduled preventative maintenance and calibration performed by a qualified balance technician every six (6) months.

5.2.7 Record any repair or maintenance service in a balance maintenance and calibration logbook. This includes scheduled as well as emergency service.

5.2.7 At the time of each six (6) month scheduled calibration, the technician must affix a sticker to the balance, indicating date calibrated and next due calibration date. The sticker should also contain the name of the service organization and the initials of the technician who performed the calibration.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Top-Loading Electronic Balances**	NUMBER: **009**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To assure reliable performance of top-loading electronic laboratory balances.

2.0 SCOPE:

2.1 Electronic top-loading balances.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors

4.0 FREQUENCY:

4.1 Monthly

5.0 PROCEDURE:

5.1 Materials

5.1.1 Calibration weights, ASTM Class 1 or better, ranging from 1 gm to balance capacity to bracket weights measured during normal balance operation.

5.2 Calibration Check

5.2.1 Check the accuracy of each electronic top-loading balance by weighing a series of calibration weights that bracket normally used weighings. Take at least five (5) different weighings over the operational range of the balance.

5.2.2 Record the actual weight values obtained for each of the calibration weights.

5.2.3 The observed value should be within 1 percent of the individual values cited on the calibration weight.

5.2.4 Record all weighings in a balance calibration logbook.

5.2.5 If any observed weighings exceed 1 percent of a calibration weight value, take the balance out of service until it has been recalibrated and certified by a qualified balance service technician.

5.2.6 Have regularly scheduled preventative maintenance and calibration performed by a qualified balance technician every six (6) months.

5.2.7 Record any repair or maintenance service in a balance maintenance and calibration logbook. This includes scheduled as well as emergency service.

5.2.8 At the time of each six (6) month scheduled calibration, the technician must affix a sticker to the balance, indicating date calibrated and next due calibration date. The sticker should also contain the name of the service organization and the initials of the technician who performed the calibration.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of pH Meters**	NUMBER: **010**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide a detailed procedure for calibration of pH meters.

2.0 SCOPE:

2.1 All pH measuring instruments such as pH meters and potentiometric titrators.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors

4.0 FREQUENCY:

4.1 Each use

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 pH meter, capable of a two-point calibration between pH 7–10 and 7–4 units, equipped with a combination glass pH electrode.

5.2 Reagents

5.2.1 Buffer solutions: 4.0, 7.0, and 10.0 pH respectively, purchased.

5.2.2 Purified water, USP

5.3 Calibration for Expected Measurements Below pH 7.0

5.3.1 Set the pH meter temperature control to the ambient temperature.

5.3.2 Set the pH meter SLOPE control to 100 percent.

5.3.3 Immerse the electrode in pH 7.0 buffer and set the display to 7.00, using the meter's CALIBRATE knob.

5.3.4 Rinse the electrode with purified water and wipe dry with a soft tissue.

5.3.5 Immerse the electrode in pH 4.0 buffer, and using the meter's SLOPE control, adjust the display to read pH 4.00.

5.3.6 Repeat Step 5.3.4.

5.3.7 The pH meter is now ready for measurements of pH 7.0 or less.

5.4 Calibration for Expected Measurements Above pH 7.0

5.4.1 Set the pH meter temperature control to the ambient temperature.

5.4.2 Set the pH meter SLOPE control to 100 percent.

5.4.3 Immerse the electrode in pH 7.0 buffer and set the display to 7.00, using the meter's CALIBRATE knob.

5.4.4 Rinse the electrode with purified water, and wipe dry with a soft tissue.

5.4.5 Immerse the electrode in pH 10.0 buffer, and using the meter's SLOPE control, adjust the display to read pH 10.00.

5.4.6 Repeat Step 5.4.4.

5.4.7 The pH meter is now ready for measurements of pH 7.0 or greater.

5.5 Documentation

5.5.1 Each time a calibration is performed, record the following information in a pH meter calibration logbook:

5.5.1.1 Date.

5.5.1.2 Calibrated by.

5.5.1.3 pH Meter identity (which meter).

5.5.1.4 Catalog number, lot number and expiration data of purchased buffer solutions.

5.5.1.5 Any slope adjustment and the value of the slope in percent.

5.5.1.6 Any repairs or reconditioning of meter or electrodes.

5.6 Acceptance Criteria

5.6.1 Slope adjustment cannot be more than 98–102 percent.

5.6.2 If the slope adjustment is out of the 98–102 percent range, then recondition or change the electrode, and/or use fresh buffer solutions, and then recalibrate the meter.

5.6.3 If the meter cannot be calibrated, take it out of service and send it out for repair.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of UV/Visible Spectrophotometers**	NUMBER: **011**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for in-house calibration of UV/Visible spectrophotometers.

2.0 SCOPE:

2.1 Double and single beam scanning UV/Visible spectrophotometers.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Every six (6) months and/or after instrument service.

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 UV/Visible spectrophotometer capable of reading 200–700 nm with 1-cm silica cuvettes.

5.2 Reagents

5.2.1 Holmium oxide filter standard, NIST traceable.

5.2.2 UV standards—USP or certified house standards that have absorption maxima that bracket those wavelengths used in routine analytical work. For example, if UV scans are performed over the range of 220–280 nm, then select standards having absorption maxima of about 220 nm, 254 nm, and 280 nm respectively.

5.3 Wavelength Accuracy Check

5.3.1 Prepare the instrument for operation as per manufacturer's instructions.

5.3.2 Scan a Holmium Oxide Standard Filter from 700–200 nm versus air.

5.3.3 The absorption bands should be seen at 279.0, 287.0, 333.5, 360.5, 418.5, 445.5, 453.5, 460.0, and 536.0 nm. The observed bands should be within + 0.5 nm of the wavelengths indicated.

5.4 UV Linearity Check

5.4.1 For each of the UV standards selected in 5.2.2, accurately prepare a solution in a suitable solvent having an absorbance in the range of 0.4–0.8 absorbance units when measured in 1-cm cells versus the solvent used to prepare the standard solution.

5.4.2 The standard solutions prepared in 5.4.1 are referred to as working standards.

5.4.3 For each UV standard, prepare five (5) standards that are at concentrations of 50, 75, 100, 125, and 150 percent of working standard strength.

5.4.4 For each set of standard solutions, measure the absorbance of each level in 1-cm cells versus the solvent used for preparation.

5.4.5 For each set of standards, plot absorbance versus concentration on a linear scale.

5.4.6 Perform a linear regression on each of the standard curves.

5.4.7 The linear correlation coefficient for each curve must be no less than 0.999.

5.5 Acceptance

5.5.1 If any of the limits cited above for wavelength accuracy or linearity do not meet stated criteria, the instrument must be taken out of service until such time that it is repaired and recalibrated.

5.6 Scheduled Maintenance

5.6.1 A yearly preventative maintenance and calibration is to be performed by an outside source, such as the instrument manufacturer.

5.7 Documentation

5.7.1 Record holmium oxide wavelength accuracy data, including the holmium oxide scan, in a UV/Visible spectrophotometer maintenance and calibration logbook.

5.7.2 Record all linearity data such as absorbencies, standard preparation, standard lot numbers, and linearity data in a UV/Visible spectrophotometer maintenance and calibration logbook.

5.7.3 Record both scheduled and emergency service calls in a UV/Visible spectrophotometer maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Infrared Spectrophotometers**	NUMBER: **012**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for in-house calibration of infrared spectrophotometers.

2.0 SCOPE:

2.1 Dispersion, ratio recording, and Fourier transform infrared spectrophotometers.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Monthly and/or after instrument service.

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 Infrared spectrophotometer.

5.2 Reagents

5.2.1 Polystyrene reference strip.

5.3 Wavelength Accuracy Check

5.3.1 Prepare the instrument for operation as per manufacturer's instructions.

5.3.2 Scan a polystyrene reference strip from 2.5 μm to 15 μm versus air, using an unattenuated reference beam.

5.3.3 The resulting infrared spectrum should exhibit absorption bands only at the same wavelengths as that of a standard polyethylene reference spectrum. Such a spectrum may be taken from literature.

5.4 Acceptance

5.4.1 If any of the limits cited above for wavelength accuracy do not meet stated criteria, the instrument must be taken out of service until such time that it is repaired and recalibrated.

5.5 Scheduled Maintenance

5.5.1 A yearly preventative maintenance and calibration is to be performed by an outside source such as the instrument manufacturer.

5.6 Documentation

5.6.1 Record polyethylene spectra, along with a copy of a standard polyethylene spectrum, in an IR spectrophotometer maintenance and calibration logbook.

5.6.2 Record both scheduled and emergency service calls in a spectrophotometer maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of High Pressure Liquid Chromatographs**	NUMBER: **013**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 4
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for in-house calibration of high pressure liquid chromatographs (HPLC).

2.0 SCOPE:

2.1 All HPLC systems used for official analytical work.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Perform calibration of HPLC system components quarterly or when system service is performed, such as a lamp or seal change. Perform maintenance procedures yearly, or sooner, if needed.

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 HPLC system consisting of a solvent delivery system, variable wavelength UV/Visible detector, and autosampler.

5.1.2 Normal laboratory glassware.

5.1.3 UV standards–USP or certified house standards that have absorption maxima that bracket those wavelengths used in routine analytical work. For example, if HPLC methods are performed using a range of wavelengths from 220 to 280 nm, then select standards having absorption maxima of about 220 nm, 254 nm, and 280 nm respectively.

5.1.4 Reverse phase column, C-18, 5-micron particle size, 150 mm x 4 mm.

5.1.5 Stopwatch.

5.1.6 Graduate cylinder: 10.0 mL.

5.2 Reagents

5.2.1 Mobile phase for each of the methods needed to use the respective UV standards selected in 5.1.3.

5.3 Pump Calibration Check

5.3.1 Using a stopwatch and 10 mL graduate cylinder, measure the flow rate over a five-minute period each at several flow rates that bracket the flow rates used in routine analytical work such as 0.5, 1.0, 1.5, and 2.0 mL per minute .

5.3.2 The measured flow at each speed should be within ± 10 percent of the expected value.

5.3.3 Flows should be measured under load, i.e., while pumping mobile phase through an analytical column. Use a viscous mobile phase such as water/methanol, 3:1, v/v.

5.4 Variable Wavelength Detector Check

5.4.1 For each of the UV standards selected in 5.1.3 and using the standard preparation procedure for its assay, prepare a stock solution of active ingredient at 10 times the working concentration in specified diluent.

5.4.2 For each of the UV standards selected in 5.1.3 and using the following table, accurately dispense the appropriate volumes into separate 100.0 mL volumetric flasks, and dilute each flask to the mark with diluent solution.

5.4.3 Stopper each of the 100 mL volumetric flasks, and invert several times to mix.

5.4.4 For each wavelength, make five (5) injections of each standard solution, and record the peak areas for each injection.

DETECTOR LINEARITY SOLUTIONS	
% WORKING CONCENTRATION	**STOCK STANDARD SOLUTION (milliliters)**
50	5.0
75	7.5
100	10.0
125	12.5
150	15.0

5.4.5 For each wavelength, plot the average peak area obtained for each solution versus its corresponding theoretical concentration.

5.4.6 Perform a linear regression analysis on each curve of area units versus concentration.

5.4.7 Each linear curve must have a minimum correlation coefficient of 0.999, and the percent relative standard deviation (%RSD) for any set of five (5) injections may not exceed 2.0 percent.

5.5 Autosampler Calibration Check

5.5.1 Using the 100 percent working concentration of any one of the standards used in 5.4, inject three (3) replicate injections each at different injection volumes, using injection volumes that bracket those used for routine analytical work, such as 5.0, 10.0 and 20.0 microliters.

5.5.2 Calculate the %RSD of the triplicate injections for each of the five standards that were injected.

5.5.3 The %RSD of each set of triplicate injections may not exceed 2.0 percent.

5.5.4 Plot the average peak area obtained for each standard solution versus its corresponding theoretical concentration.

5.5.5 Perform a linear regression analysis on each curve of area units versus concentration.

5.5.6 Each linear curve must have a minimum correlation coefficient of 0.999.

5.6 Acceptance

5.6.1 If any of the limits cited above for injection precision and injection linearity do not meet stated criteria, the appropriate component of the instrument must be taken out of service until such time that it is repaired and recalibrated.

5.7 Scheduled Maintenance

5.7.1 A yearly preventative maintenance and calibration is to be performed by an outside source such as the instrument manufacturer.

5.8 Documentation

5.8.1 Record wavelength linearity, injection precision and linearity, and flow calibration data in an HPLC maintenance and calibration logbook.

5.8.2 Record both scheduled and emergency service calls in an HPLC maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Validation of Integrators And Data Reduction Systems**	NUMBER: **014**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for verification of chromatography integrators and data systems.

2.0 SCOPE:

2.1 All electronic integrators and data systems used for peak integration and chromatography data processing.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors. Signal calibration to be performed by outside instrument service company such as the instrument vendor.

4.0 FREQUENCY:

4.1 One time only for each integrator and data system used by the laboratory.

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 Signal generator: NIST traceable, capable of electronic peak generation and simulation.

5.1.2 Integrators or data reduction system.

5.2 Reagents

5.2.1 None

5.3 Integration Accuracy (Electronics)

5.3.1 Connect a signal generator output to the integrator or data system inputs normally used for HPLC or GC signal input.

5.3.2 Generate peaks that cover the operational span of the integrator and record the resulting area units. For example, if an integrator has a -500 mv to +1000 mv operating range, then inject a series of peak signals to cover that range. Use at least 10 points along the span.

5.3.4 For each peak, the area units obtained should correspond to the value of the injected signal. For example, if the integrator or data system has a specification that states its output in microvolts per area unit, then the area units times microvolts divided by 1000 should equal the millivolt input from the signal generator for each of the electronically injected peaks within the integrator's or data system's stated limits.

5.3.5 Plot each of the peak area units versus signal millivolts.

5.3.6 Perform a linear regression analysis on the plot generated in 5.3.5.

5.3.7 The resulting linear correlation coefficient must be no less than 0.999.

5.4 Calculation Accuracy (After Verification of Electronics)

5.4.1 Perform a routine HPLC or GC analysis of each type normally run by the laboratory, such as area normalization, external standard, and internal standard.

5.4.2 Calculate the results of each analysis manually from integrator or data system area units and compare them with results calculated by the integrator or data system. The results should be identical.

5.4.3 Perform 5.4.2 at least 12 times for each type of calculation mode utilized in normal analytical work.

5.5 Acceptance

5.5.1 If any of the criteria cited above are not met, the instrument must be taken out of service until such time that it is repaired and recalibrated.

5.6 Scheduled Maintenance

5.6.1 None: Chromatography calibrations confirm proper operation.

5.7 Documentation

5.7.1 Record all signal verification and calculation verification data in an integrator/ data system logbook.

5.7.2 Record any emergency service calls in an integrator/data system logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Flame Atomic Absorption Spectrophotometers**	NUMBER: **015**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for calibration of flame atomic absorption spectrophotometers.

2.0 SCOPE:

2.1 All flame atomic absorption spectrophotometers.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Every six (6) months: outside instrument service.

4.2 Each use: linearity calibration.

5.0 PROCEDURE:

5.1 Apparatus

5.1.1 Flame atomic absorption spectrophotometer.

5.1.2 That stated in individual analytical method monographs.

5.2 Reagents

5.2.1 Those stated in individual analytical method monographs.

5.3 Six (6) Month Complete Certification

5.3.1 Vendor is to perform a complete instrument preventative maintenance and calibration on each instrument.

5.4 Per Use Linearity Check

5.4.1 Each time a quantitative analytical procedure is performed, a linearity check must be done as part of the preparation of a standard curve for the analyte under analysis.

5.5 Acceptance

5.5.1 Six (6) month vendor service: Instrument must meet all listed performance specifications to include all mechanical, electronic and optical components.

5.5.2 Daily linearity: Must meet criteria set forth in individual method monographs as defined by the method validation for that method or by compendial criteria.

5.5.3 An instrument that is not in conformance with defined operational parameters must be taken out of service until it is repaired and certified by the instrument vendor or other qualified service organization.

5.6 Scheduled Maintenance

5.6.1 As per 5.5.1 plus user maintenance as recommended in the instrument operating manual, such as changing O-rings, cleaning nebulizer tubing, and changing lamps.

5.7 Documentation

5.7.1 Record all six (6) month service data in an atomic absorption spectrophotometer maintenance and calibration logbook.

5.7.2 Record all linearity data, such as absorbancies, standard preparation, standard lot numbers, and linearity data in laboratory notebooks or worksheets when performing an analytical procedure.

5.7.3 Record any emergency service calls in an atomic absorption spectrophotometer maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Ovens**	NUMBER: **016**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for calibration of laboratory ovens.

2.0 SCOPE:

2.1 All laboratory ovens used for analytical work.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Yearly: outside instrument service.

5.0 PROCEDURE:

5.1 Calibration and Usage

5.1.1 Using NIST traceable thermometers or thermometers whose calibration is traceable to NIST traceable thermometers, measure the temperature of the oven, using at least six (6) temperatures that have been selected to be evenly spread over the working range of the oven temperatures used by the laboratory, 60–200 degrees centigrade, for example.

5.1.2 Plot a curve of oven temperature setpoint versus actual observed temperature.

5.1.3 Use the resulting curve as a calibration curve for setting desired working temperatures.

5.1.4 In addition, keep a calibrated thermometer mounted in the oven as an on-going check of temperature accuracy.

5.2 Acceptance

5.2.1 If the oven cannot achieve or maintain normal operating temperatures, it must be taken out of service until repaired and recalibrated.

5.3 Scheduled Maintenance

5.3.1 As per Section 4.0.

5.4 Documentation

5.4.1 Record all yearly calibration and/or service data in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

5.4.2 Record any emergency service in an oven/furnace/refrigerator/thermometer calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Furnaces**	NUMBER: **017**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for calibration of laboratory furnaces.

2.0 SCOPE:

2.1 All laboratory furnaces used for analytical work.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Yearly: outside instrument service.

5.0 PROCEDURE:

5.1 Calibration and Usage

5.1.1 Using NIST traceable temperature probes or temperature probes whose calibration is traceable to NIST traceable temperature probes, measure the temperature of the furnace, using at least six (6) temperatures that have been selected to be evenly spread over the working range of the furnace temperatures used by the laboratory, 400–1000 degrees centigrade, for example.

5.1.2 Plot a curve of furnace temperature setpoint versus actual observed temperature.

5.1.3 Use the resulting curve as a calibration curve for setting desired working temperatures.

5.1.4 In addition, keep a calibrated temperature probe or thermocouple mounted in the furnace as an ongoing check of temperature accuracy.

5.2 Acceptance

5.2.1 If the furnace cannot achieve or maintain normal operating temperatures, it must be taken out of service until repaired and recalibrated.

5.3 Scheduled Maintenance

5.3.1 As per Section 4.0.

5.4 Documentation

5.4.1 Record all yearly calibration and/or service data in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

5.4.2 Record emergency service calls in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Thermometers**	NUMBER: **018**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for calibration of laboratory thermometers.

2.0 SCOPE:

2.1 All laboratory thermometers used for analytical work.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Yearly: outside instrument service—send out for calibration.

5.0 PROCEDURE:

5.1 Calibration and Usage

5.1.1 Specify that, using NIST traceable thermometers, each laboratory thermometer submitted for calibration is to be checked using at least three points that bracket the thermometer's normal operating temperatures, such as 0–200 degrees centigrade.

5.1.2 Plot a curve of observed thermometer temperature versus actual temperature.

5.1.3 Use the resulting curve as a calibration curve for correcting temperatures observed when using laboratory thermometers.

5.1.4 The calibrated thermometers should be used to check such devices as water baths, ovens, and refrigerators.

5.2 Acceptance

5.2.1 None: Use calibration curve. Any thermometer that breaks or does not respond to temperature variation should be discarded.

5.3 Scheduled Maintenance

5.3.1 As per Section 4.0.

5.4 Documentation

5.4.1 Record all yearly calibration data in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

5.4.2 Each thermometer should be numbered and identified by its number whenever it is used, either for calibration or for routine temperature measurements.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Refrigerators**	NUMBER: **019**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for calibration of laboratory refrigerators.

2.0 SCOPE:

2.1 All laboratory refrigerators used for analytical work.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Yearly: outside instrument service.

5.0 PROCEDURE:

5.1 Calibration and Usage

5.1.1 Using NIST traceable thermometers or thermometers whose calibration is traceable to NIST traceable thermometers, measure the temperature of the refrigerator, using at least six (6) temperatures that have been selected to be evenly spread over the working range of the refrigerator temperatures used by the laboratory, 0–20 degrees centigrade for example.

5.1.2 Plot a curve of refrigerator temperature setpoint versus actual observed temperature.

5.1.3 Use the resulting curve as a calibration curve for setting desired working temperatures.

5.1.4 In addition, keep a calibrated thermometer mounted in the refrigerator as an ongoing check of temperature accuracy.

5.2 Acceptance

5.2.1 If the refrigerator cannot achieve or maintain normal operating temperatures, it must be taken out of service until repaired and recalibrated.

5.3 Scheduled Maintenance

5.3.1 As per Section 4.0.

5.4 Documentation:

5.4.1 Record all yearly calibration and/or service data in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

5.4.2 Record emergency service calls in an oven/furnace/refrigerator/thermometer maintenance and calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Management of Analytical Standards**	NUMBER: **020**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for management of analytical standards.

2.0 SCOPE:

2.1 All primary analytical reference standards, including but not limited to compendial assay, titrimetric, thermometric, and spectrophotometric standards.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Continuous and ongoing.

5.0 PROCEDURE:

5.1 General

5.1.1 USP Standards are required for all compendial monograph work. These can be purchased from the US Pharmacopeial Convention. USP standards should be stored under recommended storage conditions.

5.1.2 Only the current regulatory lot should be used. Current lot numbers are listed in the Pharmacopeial Forum or in the USP standards catalog.

5.1.3 In lieu of USP standards, house standards, assayed versus USP standards, may be used. House standards should be recertified every six months versus a current regulatory lot of USP standard.

5.1.4 When it is not possible to obtain USP or house standards, or some other certified chemically pure standards, such as BP standards, then purchased prepared standards may be used.

5.2 Receipt of Standards

5.2.1 Upon receipt of a standard, the name, lot number, and date received should be entered into a standards log book.

5.2.2 The standard should then be stored in a secure location into which access is limited only to laboratory personnel having management authority.

5.3 Control of Standards

5.3.1 When a standard is needed for analytical work, it should be issued to the analyst by a supervisor. The analyst should sign out the standard, and upon return, log the amount used and notebook reference to actual weighings of the standard. After use, a supervisor must return the standard to its secure location.

5.3.2 A periodic inventory should be taken and documented to assure that only current lots are in the system. Out-of-date lots of standard must be destroyed.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Certification of House Standards**	NUMBER: **021**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for certifying house standards as analytical reference standards.

2.0 SCOPE:

2.1 All materials to be used as house standards, including but not limited to raw materials and purchased reagents.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Every six (6) months.

5.0 PROCEDURE:

5.1 Equipment

5.1.1 That specified in the monograph applicable to the method used to certify a potential house standard against a primary reference standard.

5.2 Reagents

5.1.2 Those specified in the monograph applicable to the method used to certify a potential house standard against a primary reference standard.

5.3 Analysis of House Standard

5.3.1 Using the potential house standard as a sample, perform the standard preparation and sample preparation, and determine the purity of the house standard versus the primary reference standard according to the procedure in the monograph that is being used.

5.3.2 Perform the analysis in triplicate, using separate standard and sample weighings for each determination.

5.3.3 Calculate the assay result of the house standard versus primary reference standard for each of the three individual determinations.

5.3.4 Calculate the average and percent relative standard deviation (%RSD) for the three assays.

5.4 Acceptance

5.4.1 If the %RSD is 2.0 or less, then the potential house standard can be used as a reference standard for analytical work, using its average assay value as its purity.

5.5 Documentation

5.5.1 Label the house standard with purity, date certified, expiration date, and reference to primary data that support the certification.

5.5.2 Record all assay data in hardbound notebooks or laboratory worksheets.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration of Karl Fisher Apparatus**	NUMBER: **022**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for standardization of Karl Fisher reagent for moisture analysis.

2.0 SCOPE:

2.1 Karl Fisher reagent used with automatic or manual Karl Fisher titration units.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Each use.

5.0 PROCEDURE:

5.1 Equipment

5.1.1 Karl Fisher titration setup, manual, or automatic with amperometric endpoint detection.

5.2 Reagents

5.1.1 Karl Fisher reagent, pyridine or non-pyridine based.

5.1.2 Methanol, anhydrous.

5.1.3 Water, purified.

5.3 Standardization of Karl Fisher Reagent

5.3.1 Set up the Karl Fisher apparatus as per manufacturer's instructions.

5.3.2 Add 100 mL of anhydrous methanol to the titration vessel.

5.3.3 Titrate with Karl Fisher reagent to blank out the methanol.

5.3.4 Accurately transfer one (1) drop of water (about 50 mg) from a small dropping bottle into the vessel containing blanked methanol. Obtain an accurate weight of water by weighing the dropping bottle before and after the addition of water to the methanol.

5.3.5 For manual setups, titrate the water with Karl Fisher reagent to the same color as that of the blanked methanol prior to addition of water.

5.3.6 For automated units, titrate the water with Karl Fisher reagent to the same amperage as that of the blanked methanol prior to addition of water.

5.3.7 Perform the standardization in triplicate.

5.3.8 Calculate the water equivalence factor for the Karl Fisher reagent for each titration as follows:

$$\frac{\text{mg of water}}{\text{mL KF Reagent}} = \text{Water equivalence factor (mg/mL)}$$

5.3.9 Average the three standardization values.

5.3.10 If the %RSD of the three standardizations is 1.0 or less, the average water equivalent factor can be used for titration of samples for water content.

5.3.11 If the %RSD of the three standardizations is greater than 1.0, the standardizations must be repeated until the criterion specified in 5.3.10 is met.

5.4 Documentation

5.4.1 Record all standardization data in a Karl Fisher Calibration logbook.

5.5.2 Record all service on Karl Fisher units in a Karl Fisher Calibration logbook.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason- N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Handling of Test Solutions, Indicator Solutions, Buffer Solutions, Solvents and Dry Chemicals**	NUMBER: **023**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To describe the basic requirements for storage, labeling, and outdating of test solutions, indicator solutions, buffer solutions, solvents, and dry chemicals.

2.0 SCOPE:

2.1 All test solutions, indicator solutions, buffer solutions, solvents, and dry chemicals.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Continuous, ongoing.

5.0 PROCEDURE:

5.1 Test Solutions and Indicators

5.1.1 Both purchased and laboratory prepared solutions should be labeled with name, date of preparation, and expiration date. Purchased solution should be marked with date received.

5.1.2 If a laboratory prepared solution is not a USP solution, a reference to the preparation procedure should also be included on the label.

5.1.3 Store under recommended storage conditions.

5.2 Buffer solutions

5.2.1 Purchased buffer solutions should be marked with the date received and may not be used beyond their labeled expiration date.

5.2.2 Laboratory prepared solutions should be labeled with name, date of preparation, and expiration date.

5.2.3 If a laboratory prepared solution is not a USP solution, a reference to the preparation procedure should also be included on the label.

5.2.4 Store under recommended storage conditions.

5.3 Dry Chemicals and Solvents

5.3.1 Dry chemicals and solvents should be labeled with a receiving date and an expiration date (usually one year) and stored under recommended storage conditions.

5.3.2 Flammable or combustible solvents should be stored in special solvent cabinets designed for storage of such materials. Be sure that materials, such as acids, bases, oxidizers, and peroxides, are properly stored and segregated from materials with which they may interact.

5.4 General

5.4.1 Periodic inventories should be taken on all of the above to avoid having expired materials in service.

5.5 Documentation

5.5.1 A logbook should be maintained for inventory, receipt, expiration date, and removal of all solutions, dry chemicals, and solvents.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Preparation and Standardization of Volumetric Test Solutions**	NUMBER: **024**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To describe the general procedure for preparation and standardization of volumetric test solutions.

2.0 SCOPE:

2.1 All volumetric test solutions.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Each time a volumetric test solution is prepared or standardized.

5.0 PROCEDURE:

5.1 Preparation and Standardization

5.1.1 Prepare and standardize volummetric test solutions as per USP procedures specified under "Volumetric Solutions," USP 23, Pages 2057–2063, or per an in-house monograph.

5.1.2 Perform standardizations in triplicate.

5.1.3 Standardization is acceptable if the percent relative standard deviation (%RSD) between the individual standardization values is ≤ 0.5.

5.1.4 Label the volumetric test solution with name, strength (normality, molarity, or molality), date standardized, expiration date, and reference to raw data and calculations for the standardizations.

6.0 SAMPLE MONOGRAPH (Preparation and Standardization of 0.1N NaOH):

6.1 Equipment

6.1.1 Normal laboratory glassware.

6.1.2 Hot plate.

6.1.3 Clear plastic wrap.

6.2 Reagents

6.2.1 Sodium hydroxide, reagent grade.

6.2.2 Potassium biphthalate, certified primary standard grade.

6.2.3 Phenolphthalein indicator solution, 1% w/v in absolute ethanol.

6.2.4 Purified water, USP (hereafter referred to as "water").

6.3 Procedure

6.3.1 Using a 1500-mL beaker, dissolve 4.0 grams of reagent grade NaOH in 1000 mL of water.

6.3.2 Bring the solution to a boil on a hot plate, and boil for five (5) minutes.

6.3.3 Remove the beaker containing the NaOH solution from the hot plate, cover the beaker with clear plastic wrap, and allow the solution to cool to room temperature.

6.3.4 Filter the resulting solution through glass wool into a 1-liter polyethylene bottle for storage. Keep the bottle capped when not in use, avoiding exposure to the air.

6.3.5 Accurately weigh about 600 mg of primary standard potassium biphthalate into a 250 mL Erlenmeyer flask. Add about 100 mL of water, and stir to dissolve the primary standard.

6.3.6 Add four (4) drops of phenolphthalein indicator solution and titrate with the prepared sodium hydroxide solution to a pink color that persists for at least 30 seconds.

6.3.7 Record the volume of titrant used.

6.3.8 Similarly, titrate a blank consisting of all of the above reagents but omitting the primary standard.

6.4 Calculations

$$N = \frac{\text{Weight of Standard in Grams}}{(\text{mL Titrant} - \text{mL Blank}) \times 0.2042}$$

NOTE: 0.2042 = milliequivalent wt of Standard

7.0 HISTORY:

7.1 REVISION 0: Supersedes - Original
Reason - N/A

References

USP 23/NF 18, Rockville: United States Pharmacopeial Convention, Inc.

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Instrument Operating Procedures**	NUMBER: **025**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 1
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a mechanism by which operating procedures for analytical instruments and other laboratory apparatus are to be documented.

2.0 SCOPE:

2.1 All analytical instrumentation and laboratory apparatus.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Upon receipt of any analytical instrumentation or laboratory apparatus.

5.0 PROCEDURE:

5.1 Monograph Option

5.1.1 Prepare a monograph in standard SOP format (See SOP 001) that describes, in detail, all procedures for operation and maintenance of the subject equipment.

5.2 User Manual Reference Option

5.2.1 Prepare an SOP, in standard SOP format (See SOP 001), that references specific sections of the instrument or apparatus user's manual dealing with specific instructions for operation and maintenance of the subject equipment.

5.2.2 Attach copies of all referenced sections of the user's manual as part of the SOP. The SOP itself acts as a cover sheet for operation and maintenance of the subject instrument.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Standard Practices for Chromatography Analysis**	NUMBER: **026**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 4
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define overall parameters for quantitative analysis using chromatographic procedures.

2.0 SCOPE:

2.1 All HPLC and gas chromatography analyses.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors.

4.0 FREQUENCY:

4.1 Each time a chromatographic analysis is performed.

5.0 PROCEDURE:

5.1 Materials and Equipment

5.1.1 An HPLC system consisting of, at minimum, a solvent delivery system, UV/Visible detector (fixed wavelength filter, variable wavelength or diode array type), mobile phase, autosampler, and an integrator or data reduction system, or a gas chromatography system consisting of, at minimum, an injection port (packed or capillary), detector (FID, TCD, or other), column oven, proportional temperature controls, supply gases, autosampler, and integrator or data reduction system.

5.1.2 Analytical column specified in method monograph.

5.2 Reagents

5.2.1 As specified in individual method monograph.

5.3 Chromatographic Conditions

5.3.1 As specified in individual method monographs.

5.4 Instrument Startup

5.4.1 Refer to Instrument Operating Procedure for instrument being used.

5.5 System Suitability

5.5.1 Perform at the beginning of the analytical run.

5.5.2 Collect the chromatograms and readouts for the first five (5) injections of standard.

5.5.3 Calculate the %RSD of the area units for each peak of interest (analyte) and for any internal standard peaks.

5.5.4 If the %RSD for all peaks is 2.0 or less, proceed with analysis.

5.5.5 If the %RSD for any of the analytes is greater than 2.0, continue injecting standards until five (5) consecutive injections meet the %RSD criteria cited in 5.5.4.

5.5.6 Preserve the system suitability data with the analytical data for the analysis being performed.

5.6 Procedures for Standard and Sample Injections

5.6.1 After establishment of system suitability, the injection scheme for samples and standards is as follows:

Standard (standard preparation #1)

Check standard as sample (standard preparation #2)

Sample

Sample

Standard

Three samples

Standard

Continue to bracket three samples with a standard, ending with a standard.

5.6.2 The result of each component in the check standard versus the calibration standard must be within 1 percent relative to the amounts weighed into the check standard. Note: The calibration standard and check standard are separate weighings (standard preparations) of the same analytical standard.

5.6.3 If the check standard is within limits, continue with the analytical run.

5.6.4 If the check standard is not within limits, remake both standards and start over at step 5.5.

5.6.5 In addition to the check standard meeting its limits, each standard injected during the run must have a cumulative %RSD of no greater than 2.0 for each analyte when averaged with all preceding standards, including those used for system suitability.

5.6.6 If a standard injected during the run does not meet the 2.0% RSD, as specified in 5.6.5, then restart the analysis, beginning with system suitability, and start the sample run with the three samples immediately preceding the standard that failed to meet the cumulative %RSD criteria.

5.7 Evaluation of Chromatography

5.7.1 For each sample, if each injection produces in-spec results for each component, the average of the two can be accepted as the final result, provided the criteria for bracketing standards are met.

5.7.2 If one injection is in spec for one or more components and the second is not out of the same vial, the out-of-spec injection can be treated as an injection error and the sample reinjected in duplicate, bracketed by standards, at the end of the run, using the same vial.

5.7.3 If both injections from the same vial produce out-of-spec results for one or more components, the sample is treated as an OOS (Out-of-Spec) result and must be subjected to an informal laboratory investigation as per Standard Operating Procedure 033, "Laboratory Failure Investigations."

5.7.4 Changes in expected retention times, distorted (non-symmetrical) peak shapes, broadening or tailing peaks, no peaks, abnormally small or large peaks, baseline upsets or aberrations, and wandering baseline are some of the more common reasons for poor chromatography and poor results. These are also reasons to classify an OOS as explainable. The following criteria must be met for good chromatography:

- Baseline code = Baseline-Baseline for *all* peaks
- Beginning and ending markers for all peaks
- No baseline pegs to extreme left or right side of paper
- Clean baseline, no shifts, oscillations, or extra peaks
- No tailing peaks beyond limits of tailing factors specified in individual method monographs

5.7.5 When quality of chromatography starts to deteriorate, perform instrument and/or column service needed to restore normal operating conditions.

5.8 Instrument Shutdown

5.8.1 Refer to user's manual for the instrument being used.

5.8.2 For HPLC systems, when not in use, it is desirable to maintain a low flow of mobile phase (0.1 mL/min) through the column in order to prevent column plugging, and if the instrument will be idle for an extended period of time, such as overnight or on weekends, the UV lamp should be turned off.

5.8.3 For gas chromatography systems, it is desirable to reduce carrier gas flow rate to a minimum flow (5 cc/min) and to reduce the column oven temperature to about 40–50 degrees centigrade when the instrument is not in use.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Sample Analytical Monograph (Single Test Style)—Assay of Acetaminophen Granulations**	NUMBER: **027**	REV: **1**
WRITTEN BY:	DATE:	PAGE 1 OF 4
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide an in-house monograph for determination of acetaminophen purity in 90% acetaminophen granulations.

2.0 SCOPE:

2.1 Assay of acetaminophen granulations using a modification of the USP 23 procedure for assay under "Acetaminophen Capsules."

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors and analysts.

4.0 FREQUENCY:

4.1 Each assay determination.

5.0 PROCEDURE:

5.1 Reagents and Apparatus

5.1.1 Acetaminophen USP or House Reference Standard.

5.1.2 Methanol, anhydrous, HPLC-grade.

5.1.3 Deionized water.

5.1.4 Ultrasonic water bath.

5.1.5 HPLC system, consisting of a pump, autosampler, UV detector and integrator.

5.1.6 Volumetric flasks, 250-mL.

5.1.7 0.45 micron disposable filters, Acrodisc™ or equivalent.

5.1.8 Disposable 5 mL syringes, luer lok™.

5.1.9 HPLC sample vials, disposable.

5.1.10 Analytical balance, capable of reading to 0.01 mg.

5.2 Chromatographic Conditions

5.2.1 Column, C18 reverse phase, 5–10 micron, 3.9 mm x 150 mm.

5.2.2 Flow rate, 1.5 mL/minute.

5.2.3 Wavelength, 254 nm.

5.2.4 Mobile phase, degassed H_2O/Methanol, 3:1 v/v.

5.2.5 Injection volume, 5 microliters.

5.2.6 Detector range, 0.5 AUFS.

5.27 Chart speed, 1 cm/minute.

5.3 Standard Preparation

5.3.1 Accurately weigh 60 mg of USP Acetaminophen Reference Standard or Acetaminophen House Standard and transfer quantitatively into a 250-mL volumetric flask, by difference, or with the aid of several milliliters of mobile phase.

5.3.2 Add 30 mL of mobile phase to the 250-mL volumetric flask containing the standard and sonicate the resulting mixture for 15 minutes.

5.3.3 Cool the contents of the 250-mL volumetric flask to room temperature. Dilute the flask to the mark with mobile phase, add a small Teflon®-coated magnetic stirring bar, and stopper and stir on a magnetic stir plate for one (1) hour.

5.3.4 Transfer a portion of the resulting solution into a disposable HPLC sample vial.

5.3.5 Prepare standards in duplicate using two (2) separate weighings.

5.4 Assay Preparation

5.4.1 Accurately weigh a quantity of sample, previously dried @ 105°C. for one (1) hour, equivalent to 60 milligrams of acetaminophen and transfer quantitatively into a 250-mL volumetric flask, by difference, or with the aid of several milliliters of mobile phase.

5.4.2 Add 30 mL of mobile phase to the 250-mL volumetric flask containing the sample and sonicate the resulting mixture for 15 minutes.

5.4.3 Cool the contents of the 250-mL volumetric flask to room temperature. Dilute the flask to the mark with mobile phase, add a small Teflon-coated magnetic stirring bar, and stopper and stir on a magnetic stir plate for one (1) hour.

5.4.4 Filter a portion of the resulting solution through a 0.45 micron Acrodisc™ filter directly into a disposable HPLC sample vial, discarding the first five (5) mL of filtrate.

5.5 Analysis

5.5.1 Inject five (5) replicate injections of a standard preparation into the chromatograph.

5.5.2 The relative standard deviation for the replicate injections should be no more than 2.0 percent. The column efficiency should be not less than 1000 theoretical plates, and the tailing factor should be no more than 2.

5.5.3 Inject two (2) replicate injections each of the duplicate standard preparations into the chromatograph and calculate the purity of standard #2 versus the response factor for standard #1. The purity of the second standard preparation should be between 99–101 percent relative to the first standard preparation.

5.5.4 Inject two (2) replicate injections of each assay preparation, bracketing the assay preparations with one of the standard preparations by injecting two (2) replicate injections of a standard preparation after every third sample (assay preparation).

5.5.5 If the cumulative standard deviation of each periodic standard, when averaged in with the initial five (5) system suitability injections plus prior periodic standard injections, is greater than 2.0 percent, then the sample results between it and the previous standard cannot be accepted. In that case, a new system suitability must be performed and the questionable samples repeated (Refer to SOP 026, "Standard Practices for Chromatographic Analyses").

5.5.6 For samples that are properly bracketed by standards, calculate the quantity of acetaminophen in the portion of granulation taken for analysis. Save all original chromatograms and raw data.

5.6 Calculations

$$\frac{A_{samp} \times W_{std}}{A_{std} \times W_{samp}} \times 100 = \%APAP\ w/w$$

Where:

A_{samp} = average areas of sample injections

A_{std} = average areas of standard injections

W_{std} = weight of standard in milligrams**

W_{samp} = weight of sample in milligrams

** For USP standards, wt = actual milligrams

** For house standards, wt = actual milligrams multiplied by (percent potency/100)

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

6.2 REVISION 1: Supersedes - 05/25/94
Reason - Modification of USP procedure

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Sample Analytical Monograph (Full Monograph Style) Potassium Chloride, USP**	NUMBER: **028**	REV: **1**
WRITTEN BY:	DATE:	PAGE 1 OF 5
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide an in-house monograph for full monograph testing of potassium chloride, USP.

2.0 SCOPE:

2.1 Potassium chloride, USP raw material incoming inspection and release testing.

3.0 RESPONSIBILITY:

3.1 Laboratory managers and supervisors and analysts.

4.0 FREQUENCY:

4.1 Each incident of testing.

5.0 PROCEDURE:

5.1 Specifications

Tests	*Acceptance Limits*
Description:	Passes Test
Identification:	Passes Test
Acidity or Alkalinity:	NMT 0.3 mL/5 gm
Loss on Drying:	NMT 1.0%
Iodide or Bromide:	Passes Test
Arsenic:	NMT 2 ppm
Calcium or Magnesium:	Passes Test
Heavy Metals:	NMT 0.001%

Sodium:	Passes Test
Assay (dried basis):	99.0–100.5%

Note: Potassium chloride reagent grade: dry at 105°C for 2 hours before using.

5.2 Description and Solubility

5.2.1 Colorless, elongated, prismatic or cubical crystals, or white granular powder. Is odorless, has a saline taste, and is stable in air. Freely soluble in water and even more soluble in boiling water; insoluble in alcohol.

5.3 LOSS ON DRYING (LOD)

5.3.1 Weigh accurately about one to two grams of the sample into a weighed, glass-stoppered weighing bottle that has been dried under the same conditions to be used in the test. Replace the stopper and reweigh the bottle and its contents.

5.3.2 By gentle sidewise shaking, distribute the contents of the bottle as evenly as possible to a depth of about 5 mm but not more than 10 mm.

5.3.3 Place the loaded bottle in the oven, remove the stopper, and dry at 105°C for 2 hours.

5.3.4 Remove the bottle from the oven, replace the stopper, allow to cool in a desiccator, and reweigh the bottle and its contents.

5.3.5 Calculate the loss on drying as follows:

$$\frac{W - Wa}{W} \times 100 = \%\text{Loss on Drying}$$

Where:

W = The weight of the sample before drying, in mg

Wa = The weight of the sample after drying, in mg

Note: Retain the LOD sample for use in the ASSAY test.

5.4 Identification

5.4.1 Weigh about 1 g of sample into a 50-mL beaker and dissolve in 20 mL of water. Filter, if necessary, through Whatman 2V filter paper.

5.4.1.1 Potassium:

Add sodium bitartrate TS to a portion of the filtered sample solution: a white crystalline precipitate is produced, which is soluble in 6 N ammonium hydroxide. The formation of the precipitate, which is usually slow, is accelerated by stirring or rubbing the inside of the test tube with a glass rod. The addition of small amounts of glacial acetic acid or alcohol also promotes precipitation.

5.4.1.2 Chloride:

Add a few drops of silver nitrate TS to a portion of the filtered sample solution: a white curdy precipitate is formed, which is soluble in a slight excess of 6N ammonium hydroxide.

5.5 Acidity and Alkalinity

5.5.1 Dissolve about 5.0 gm of sample in 50-mL of carbon dioxide-free water, add 3 drops of phenolphthalein TS; no pink color is produced. Then add 0.3 mL of 0.02 N sodium hydroxide; a pink color is produced.

5.6 Iodide or Bromide

5.6.1 Dissolve 2 gm of sample in 6 mL of water, add 1 mL of chloroform, and then add dropwise, with constant agitation, 5 mL of a mixture of chlorine TS in water (1:1): the chloroform is free from even a transient violet or a permanent orange color.

5.7 Arsenic

5.7.1 Weigh accurately, about 200 mg of sample and determine its arsenic content, following the procedure described in the SOP monograph determination of arsenic in raw materials or in USP 23, "Limit Tests," <211>, Arsenic, Method II.

5.8 Calcium or Magnesium

5.8.1 Dissolve about 500 mg of sample in 50 mL of water.

5.8.2 To 20 mL of this solution, add 2 mL each of 6 N ammonium hydroxide, ammonium oxalate TS, and dibasic sodium phosphate TS.

5.8.3 No turbidity is produced within 5 minutes.

5.9 Heavy Metals

5.9.1 Dissolve about 2.0 g, accurately weighed in 25 mL of water and perform the Heavy Metals test following the procedure described in the SOP monograph determination of heavy metals in raw materials or in USP 23, "Limit Tests," <231>, Heavy Metals, Method I.

5.10 Sodium

5.10.1 A solution (1 in 20) of the sample tested on a platinum wire, does not impart a pronounced yellow color to a non-luminous flame.

5.11 Assay

5.11.1 Weigh accurately, about 250 mg of dried sample into a 250-mL beaker.

5.11.2 Dissolve in about 150 mL of water.

5.11.3 Add 1 mL of nitric acid, and immediately titrate with 0.1 N silver nitrate VS, determining the end point potentiometrically, using silver-calomel electrodes and a salt bridge containing 4% agar in saturated potassium nitrate solution. Alternately, the titration may be performed with an automatic titrator, utilizing a combination silver-silver chloride electrode.

5.11.4 Perform a blank determination and make any necessary corrections.

5.11.5 Each mL of 0.1 N silver nitrate VS is equivalent to 7.455 mg potassium chloride. Calculate the percent potassium chloride present in the sample as follows:

$$\frac{(V - B) \times F \times 7.455 \times 100}{Wu} = \%\text{Potassium Chloride}$$

Where

V = Volume of 0.1 N silver nitrate VS, consumed by the sample, in mL.

B = Volume of 0.1 N silver nitrate VS, consumed by the blank, in mL.

F = Normality factor for 0.1 N silver nitrate VS.

Wu = Weight of the sample, in mg.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

6.2 REVISION 1: Supersedes - 05/25/94
Reason - Autotitrator suggested as alternate means of assay titration.

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Analytical Methods Validation**	NUMBER: **029**	REV: **1**
WRITTEN BY:	DATE:	PAGE 1 OF 11
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide an in-house protocol and report template for validation of analytical methods.

2.0 SCOPE:

2.1 Non-compendial release assays.

2.2 Compendial and non-compendial stability assays.

2.3 Limit tests.

3.0 RESPONSIBILITY:

3.1 Analytical R&D.

4.0 FREQUENCY:

4.1 Upon development of new assay method, or upon modification of existing assay method.

4.2 Upon development or implementation of a new limits test or modification of an existing limits test.

5.0 PROCEDURE:

5.1 Analytical Methods Validation

Validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. Performance characteristics are expressed by analytical parameters. The following table lists analytical variables and categories that are normally required for method validation in each.

5.2 Overview and Definitions

	Parameter	Assay Cat. I	Assay Cat. II		Assay Cat. III
			Quantitative	Limit Test	
1	Stability Indicating	Yes	Yes	Yes	*
2	Selectivity	Yes	Yes	Yes	Yes
3	Linearity	Yes	Yes	No	*
4	Range	Yes	Yes	*	*
5	Accuracy & Recovery	Yes	Yes	No	*
6	Precision	Yes	Yes	*	Yes
7	LOD	No	Yes	Yes	*
8	LOQ	No	Yes	Yes	*
9	Comparative Study	Yes	*	*	*
10	Ruggedness	Yes	Yes	Yes	Yes

* May be required, depending upon the nature of the specific test

CATEGORY I: Analytical methods for quantitiation of major components of bulk drug substances or active ingredients (including preservatives) in finished products.

CATEGORY II: Analytical methods to determine impurities in bulk drug substances or degradation compounds in finished products.

CATEGORY III: Analytical methods to determine performance characteristics, such as dissolution and drug release.

The validity of an analytical method can be verified only by laboratory studies. Therefore, documentation of the successful completion of such studies is a basic requirement for determining if a method is suited for its intended application.

5.3 Definition of Analytical Performance Parameters

5.3.1 Stability Indicating Aspects

The stability indicating study demonstrates baseline separation between the principal peak and the extraneous peaks (related compounds, degradation products, etc). For definition purposes 80–100% = slight degradation; 50–80% = moderate degradation; 1–50% = severe degradation; less than 1% = total degradation.

5.3.2 Selectivity

Selectivity (specificity) may often be expressed as the degree of bias obtained by analysis of samples containing added impurities, degradation products, related chemical compounds, or placebo ingredients against samples without added substances. The bias of the assay, if any, is the difference between the two groups of samples.

5.3.3 Linearity and Range

The linearity of an analytical method is its ability to produce test results which are proportional to the concentration of the analyte in the sample solutions, within the range of 50–150% of the working concentration. Linearity is usually expressed as the variance around the slope of the regression line. The importance of linearity depends on how wide-ranging the method is intended.

5.3.4 Accuracy and Recovery

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. The accuracy may be expressed as percent recovery of known, added amounts of analyte and is a measure of the exactness of the analytical method.

5.3.5 Assay Precision

The precision of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical method is usually expressed as the Relative Standard Deviation (%RSD of the assay results).

5.3.6 Limit of Detection

The limit of detection (LOD) is the lowest concentration of analyte in the target matrix that can be determined from the background to the 95% confidence level (is detectable at the most sensitive instrument settings. It may not be possible to obtain good quantitative results near the LOD).

5.3.7 Limit of Quantitation (LOQ)

The limit of quantitation is the minimum level of the analyte in the matrix that can be quantitated at the 95% confidence level. Limit of quantitation is a parameter of quantitative assay for low levels of compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals. It is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions.

5.3.8 Ruggedness

The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of normal test conditions. The method should not be prone to day-to-day or place-to-place variations. This should consist, if possible, of different laboratories, different analysts, different instruments, different reagent lots, different elapsed assay times, different assay temperatures, different days, etc. Ruggedness is a measure of test results under normal, expected operational conditions from laboratory to laboratory and from analyst to analyst.

5.3.9 Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

5.4 Determination of Analytical Performance Parameters

5.4.1 Stability Indicating Aspects and Selectivity (for HPLC assays using UV detection only)

Before starting the forced degradation tests, prepare a *10 times working* concentration solution of the placebo. Inject for at least 30 minutes and determine the contribution, if any, of the placebo to the chromatogram. The stability study consists of the following challenges: exposure to hydrogen peroxide, acid and alkali hydrolysis, and exposure to heat and light.

5.4.1.1 As per the method being validated, prepare a standard solution at 10 times the normal working concentration

5.4.1.2 Pipet 10.0 mL aliquots of sample into five (5) separate 100.0 mL volumetric flasks. Treat each as follows:

A. Add 20.0 mL of 0.5N HCl and immerse in a boiling water bath for one hour

B. Add 20.0 mL of 0.5N NaOH and immerse in a boiling water bath for one hour

C. Add 10.0 mL 10% H_2O_2 and swirl to mix and let stand 30 minutes

D. Store at 60°C for one week

E. Store under white light for one week

In addition, prepare a working concentration standard and let stand at room temperature for one week.

5.4.1.3 Dilute each sample, A–E, to the mark with RO/DI (reverse osmosis/ deionized) water. Neutralize the acid sample with 20.0 mL 0.5 N NaOH prior to dilution and the alkali sample with 20.0 mL HCl prior to dilution.

5.4.1.4 Analyze each sample versus a freshly prepared standard solution, performing the system suitability test first. Inject all preparations and allow to run for 30 minutes each. Report the separation of any extraneous peaks of degradation products from the analyte.

5.4.1.5 Peak purity techniques can be used to determine the purity of target analytes after degradation. In lieu of this, a knowledge of the degradation chemistry can be substituted, demonstrating that known degradation products can be separated from the target analyte peak, using limits tests such as HPLC or Thin Layer Chromatography.

5.4.2 Linearity and Range

5.4.2.1 Prepare standard solutions containing 50, 75, 100, 125 and 150% of the working concentration of analyte by dilution of the 10 times the working concentration standard, prepared as directed in 5.4.1.1, according to the following table:

LINEARITY STANDARDS – %WORKING CONC.	MILLILITERS OF 10 X STANDARD	FINAL VOLUME (Milliliters)
50	5.0	100.0
75	15.0	200.0
100	10.0	100.0
125	25.0	200.0
150	15.0	100.0

5.4.2.2 For each of the five (5) solutions prepared above, make three (3) replicate measurements (injections for example) of each solution and obtain the measurement output (peak areas for example).

5.4.2.3 The signal (peak area for example) obtained for each solution is plotted against its corresponding theoretical concentration, and a linear regression analysis is performed on the five (5) coordinates. The resulting plot should be linear for each analyte, at least 0.999, since it describes the line of most accurate fit to the data or potential assay bias.

5.4.2.4 Calculate the response factor, the residual factor, and the percent residual as follows:

$$\textit{Response Factor} = K_f = \frac{\textit{Observed Signal}}{\text{Concentration (mg/mL)}}$$

$$\textit{Residual} = (\textit{Observed Signal} - \textit{Calculated Signal})$$

$$\%\textit{Residual} = \frac{\textit{Residual}}{\text{Observed Signal}} \times 100$$

5.4.2.5 The response factor should demonstrate that a single point standardization level is sufficient. The residual should illustrate that the individual coordinates of the working concentration are small and randomly distributed.

5.4.2.6 The range of the method is validated by verifying that it provides acceptable precision, accuracy, and linearity when applied to sample containing analyte at the extremes of the range (e.g., 50–150%) as well as within the range of normal working concentrations.

5.4.3 Accuracy and Recovery

5.4.3.1 Using the 10 times working concentration standard prepared in 5.4.1.1, and the 10 times concentration placebo solution prepared in 5.4.1, prepare a series of matrix-containing standards according to the following table:

LINEARITY STANDARDS – %WORKING CONC.	MILLILTERS OF 10 X PLACEBO	MILLILITERS OF 10 X STANDARD	FINAL VOLUME (Milliliters)
50	10	5.0	100.0
75	20	15.0	200.0
100	10	10.0	100.0
125	20	25.0	200.0
150	10	15.0	100.0

5.4.3.2 Make five (5) replicate measurement (injections for example) of each solution and compare to a freshly prepared standard solution or standard solutions prepared at their normal working concentrations as per the method under validation.

5.4.3.3 Calculate the recovery and measurement precision (injection precision for example) of each set of measurements as follows:

The %RSD for the measurement precision is no more than 2.0 and the recovery is not more than ± 2.0% relative to the freshly prepared calibration standard or standards.

5.4.4 Assay Precision

5.4.4.1 Determine the precision of the method by preparing six (6) replicate samples from the same lot of product. Prepare samples according to the method under validation.

5.4.4.2 Make duplicate measurements of each solution versus a freshly prepared standard solution or standard solutions, prepared at their normal working concentrations as per the method under validation.

5.4.4.3 Calculate the percent of each analyte recovered from each sample.

5.4.4.4 The %RSD of the six results for each analyte should not be more than 2.0.

5.4.5 Limit of Detection (LOD)

The LOD of the analytical method is determined by comparing the test results obtained from samples with known concentrations of analyte against those of blank samples and establishing the minimum level of analyte that can be reliably detected. A signal to noise ratio of 3/1 is acceptable.

5.4.6 Limit of Quantitation (LOQ)

The LOQ of the analytical method is determined by analyzing several blank samples and calculating the RSD of this response. The standard deviation multiplied by a factor, usually 10, provides an estimate of the limit of quantitation. The limit is later validated by the analysis of samples known to be near the limit of quantitation. *Note: LOQ is approximately three times the LOD.*

5.4.7 Ruggedness

The ruggedness of an analytical method is determined by analysis of aliquots from homogeneous lots in different laboratories, by different analysts, and using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The degree of reproducibility of test results is then determined as a function of the assay variables.

5.4.8 Robustness

Robustness is determined by observing how a method stands up to slight variations in normal operating parameters. For HPLC for instance, this could be a change in flow rate or lot number of column.

5.5 Validating Changes in Analytical Methods

When the following changes occur in the method, the accompanying parameters must be revalidated.

5.5.1 Changes in the sample and standard concentration

A. Linearity and Range
B. Accuracy and Recovery
C. Precision

5.5.2 Changes in the diluent solution used for the sample and standard preparations

A. Linearity and Range
B. Accuracy and Recovery
C. Precision

5.5.3 Introducing an analyte signal for quantitation, if not previously validated

A. Linearity and Range
B. Accuracy and Recovery
C. Precision

5.5.4 For HPLC, changes in the mobile phase proportions of more than ± 5%

A. Linearity and Range
B. Accuracy and Recovery
C. Precision
D. Stability Indicating

5.5.5 Changes in the sample size, such as injection volumes in chromatography

A. Linearity and Range
B. Accuracy and Recovery
C. Precision

5.5.6 For HPLC or UV analyses, changes in spectrophotometric wavelength, perform the complete validation study.

Chromatography Only

5.5.7 Change in mode (HPLC for example, isocratic to gradient), perform the complete validation study.

5.5.8 Change in column type (e.g., C_{18} to C_8), perform the complete validation study.

5.5.9 Changes in detector (e.g., UV to refractive index), perform the complete validation study.

5.5.10 Introducing an internal standard, perform the complete validation study.

5.6 Validation Report

A validation report should be prepared and submitted for approval. It should consist of the following:

5.6.1 Summary

The summary should contain a simple statement about the results of the validation study such as, "The method for assay of Product XYZ by HPLC was found to be accurate, precise, selective, linear and stability indicating."

5.6.2 Analytical Validation Data

Analytical data should be presented in tabular and graphical form for ease of evaluation. The data presentation should show analytical results for all validation parameters described in Section 5.4, "Determination of Analytical Performance Parameters," plus residuals and all calculations used to derive results from laboratory data.

5.6.3 Discussion

Discussion should describe the outcome of the validation in detail. It should deal with any problems that were encountered and should include rationale for acceptance or rejection of the validation. Any experiments or any failing results that were repeated and then accepted need to be explained and justified.

Any deviations from acceptance criteria must be explained, and the conditions under which the method may be used (method limitations) should be clearly defined, such as only linear from 75–125% of the working concentration or meets all acceptance criteria and can be used throughout the ranges tested in the validation.

5.7 Documentation and Acceptance

5.7.1 Protocol

The validation protocol (Sections 5.1–5.5) must be approved prior to beginning a validation study.

5.7.2 Report

The validation report must be approved prior to use of the method under validation.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Laboratory Documentation Control and Distribution**	NUMBER: **029**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 4
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a procedure for control and use of laboratory documentation.

2.0 SCOPE:

2.1 Analytical methods, method validations, specifications and control schedules (testing protocol), and Standard Operating Procedures (SOPs).

3.0 RESPONSIBILITY:

3.1 Analytical R&D, Quality Control, Quality Assurance.

4.0 FREQUENCY:

4.1 Continuous, ongoing.

5.0 PROCEDURE:

5.1 Generation and Approval of New Documents

5.1.1 New analytical methods, specification sheets, and control schedules (usually specification sheets and control schedules are combined) are to be written whenever a new product is introduced for which analytical support is needed, or when a new procedure is introduced into the laboratory for which an SOP is required.

5.1.2 Analytical support includes R&D products, development products, commercial products, and all raw materials and in-process materials.

5.1.3 For analytical methods, the sequence of events is as follows:

5.1.3.1 Method is developed and put into draft form.

5.1.3.2 Method is submitted for validation. Non-compendial methods need full validation as per SOP 029. Compendial methods do not need validation for release purposes, but do need to be validated for stability indication as specified in SOP 029.

5.1.3.3 After a method has been validated, it and its validation are to be written up in final draft form and submitted for review and approvals.

5.1.4 Specifications, Control Schedules and SOPs

5.1.4.1 Specifications and control schedules are to be written such that, if they are for a compendial material, the specifications and tests performed are, at minimum, those specified in the most recent compendia or its supplements. Additional tests beyond those required may be added if needed. Tests for which no specifications are yet known, such as particle size, and where data need to be collected in order to develop a meaningful specification, the specification column of the specification sheet should read "REPORT ONLY," indicating that the test in question is for data collection purposes only and does impact upon release of material. For non-compendial materials, manufacturer's specifications may be used, using the guidelines suggested for compendial materials.

5.1.4.2 After a specification/control schedule or SOP has been prepared, it is to be submitted for review and approvals.

5.1.4.3 Specification sheets/control schedules need to have a change control authorization document attached that indicates the origination authorization as well as history of revision authorizations.

5.1.5 Review should include a detailed and critical technical review by someone with the education, training, and experience to properly conduct such a review.

5.1.6 Upon completion of review and correction of all errors, documents must be approved by at least two (2) responsible persons who have the education, training, and experience, and who have the management span of authority to exercise such approvals.

5.2 Revision of Existing Documents and Approvals Thereof

5.2.1 Analytical methods, specification sheets, control schedules (usually specification sheets and control schedules are combined), and SOPs are to be revised whenever a product specification, testing protocol, or analytical method has changed, or when an existing procedure for which an SOP is in place needs to be changed.

5.2.2 Analytical methods that have been modified or changed may need revalidation as per the criteria in SOP 029.

5.2.3 For analytical methods, the sequence of events is

5.2.3.1 Method is modified and put into draft form.

5.2.3.2 Method is submitted for either full or partial revalidation, depending upon the nature of the change.

5.2.3.3 After a method has been revalidated, it is to be written up in final draft form and submitted for review and approvals.

5.2.3.4 Specification sheets/control schedules need to have a change control authorization document attached that indicates the origination authorization as well as history of revision authorizations.

5.2.4 Specifications, Control Schedules, and SOPs

5.2.4.1 Specifications and control schedules are to be changed such that, if they are for a compendial material, the specifications and tests performed are, at minimum, those specified in the most recent compendia or its supplements. Additional tests beyond those required may be added if need be. Tests for which no specifications are yet known, such as particle size, and where data need to be collected in order to develop a meaningful specification, the specification column of the specification sheet should read "REPORT ONLY," indicating that the test in question is for data collection purposes only and does impact upon release of material. For non-compendial materials, manufacturer's specifications may be used, using the guidelines suggested for compendial materials.

5.2.4.2 After a specification/control schedule or SOP has been revised, it is to be submitted for review and approvals.

5.2.5 Review should include a detailed and critical technical review by someone with the education, training, and experience to properly conduct such a review.

5.2.6 Upon completion of review and correction of all errors, documents must be approved by at least two (2) responsible persons who have the education, training, and experience, and who have the management span of authority to exercise such approvals.

5.3 Change Control

5.3.1 For specification sheets/control schedules, a change control audit trail is maintained by way of the product change authorization.

5.3.2 For analytical methods, validations and SOPs, a change control audit trail is maintained by the History Section of each method, validation, or SOP.

5.4 Document Distribution and Usage

5.4.1 For each type of laboratory document, there should be a list of "Approved Manual Holders." These are individuals or departments that are authorized to hold a copy of a manual containing the current version of documents contained in that manual, such as analytical methods or SOPs.

5.4.2 Only the current version of each document should be in use.

5.4.3 Previous revisions of documents are to be archived for reference purposes.

5.4.4 Upon approval of a new document or new version of an existing document, it should be issued by a centralized originator, such as a document control group, to all authorized manual holders. The manual holder should sign a receipt for the new or revised document, place the new or revised document in the authorized manual, and return the previous version to the originator, who will obtain a receipt for its return These steps will assure that only current documents are in use and that all previous revisions of documents have been taken out of circulation.

5.5 Approval Signatures and Dating

5.5.1 All documents should contain the name of the author and signatures of at least one reviewer and two approvers. Signatures must be dated with the actual date signed.

5.5.2 Effective date of document must be the same date or later as that of the approver's signatures.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Calibration and Use of Dissolution Apparatus—Paddles and Baskets, USP Apparatus I and Apparatus II**	NUMBER: **031**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To provide a steering document for use and calibration of dissolution apparatus defined as USP Apparatus I and USP Apparatus II.

2.0 SCOPE:

2.1 USP monograph dissolution testing.

3.0 RESPONSIBILITY:

3.1 Laboratory manager, supervisor.

4.0 FREQUENCY:

4.1 Calibration: Every Six (6) months.

4.2 Maintenance: Before each use.

5.0 PROCEDURE:

5.1 Components

5.1.1 Daily maintenance—before each use, check level of unit, water level, warble, distance of shaft from sides of vessel, space under paddle or basket, and water bath temperature.

5.1.2 Check condition of paddles and/or baskets, and be sure that the table upon which the unit is seated is free of vibration.

5.1.3 Six month calibration—calibrate with USP prednisone calibrator tablets, nondisintegrating, and with USP salicylic acid tablets, disintegrating.

5.1.4 Check accuracy of shaft rotation as well as level of unit and centering of paddles or baskets.

5.2 Documentation

5.2.1 If the prednisone and salicylic acid calibration is suitable, then sticker the dissolution apparatus as calibrated to include the date calibrated and the calibration expiration date.

5.2.2 If the calibration fails (out of spec), then label the unit out of service until it is repaired and properly calibrated.

5.2.3 Document all maintenance and calibration done in a Dissolution Maintenance and Calibration notebook. Also, document any abnormalities found in the daily checks.

5.3 Detailed Procedure for Dissolution Testing, Including Description of Apparatus, Proper Operation of Equipment, Calibration Procedures, and Analysis of Samples

5.3.1 Refer to The United States Pharmacopeia, USP, current version, under "Physical Tests", <711>, DISSOLUTION.

5.3.2 Check current supplements to the USP for any changes in procedure <711>.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

References

USP 23/NF 18, Rockville: United States Pharmacopeial Convention, Inc.

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Auditing of Analytical Laboratory Data**	NUMBER: **032**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To offer guidelines for the auditing of laboratory data.

2.0 SCOPE:

2.1 All analytical data generated by laboratory personnel.

3.0 RESPONSIBILITY:

3.1 Laboratory managers, supervisors, and auditors.

4.0 FREQUENCY:

4.1 Upon completion of analytical work, before final approval.

5.0 PROCEDURE:

5.1 Upon completion, all laboratory data must be audited by a second person (not the analyst or analysts who did work) for accuracy, completeness, and proper sequencing.

5.2 Accuracy check should include verification of calculations, proper labeling of data and calculations, and correct cross-referencing between notebooks or worksheets, analytical methods, and ancillary documents such as chromatograms and spectra. The quality of chromatograms should also be inspected as per SOP 026, "Standard Practices for Chromatography," Section 5.7.

5.3 Completeness check should verify that all required tests have been run, recommend that material is to be released if all parameters are within specifications, and note the need for an informal laboratory investigation if any values are out of specification. A completeness check should also verify that all raw data such as sample weights and titration volumes are recorded, references to methodology are cited, and supporting documents such as chromatograms and spectra actually exist and are readily available. Chromatograms should be checked to verify that items such as system suitability, tailing factor, and resolution factor have been computed and are within acceptable limits.

5.3 Sequencing

5.3.1 The auditor must check to be sure that proper sequencing (chronology) exists. For example, check that the sample analysis was started after the sample arrived in the laboratory and that chromatography runs show a reasonable span of time for the run (not run 10 hours after a standard), and that the run numbers are sequential and match the order of samples injected during the run. The auditor must also check that notebook pages or worksheet issuances are correctly dated and make sense in terms of the dates recorded for analysis of sample.

5.4 Documentation

5.5.1 The analyst or analysts who performed the work must sign and date each notebook page or worksheet page onto which analytical data were entered.

5.5.2 Upon completion of laboratory data auditing, the auditor should countersign the notebook pages or worksheets used for the analysis, prefaced by the statement "Witnessed and Understood."

5.5 Auditor Actions

5.5.1 If errors or anomalies are noted during the audit, the auditor has the responsibility to notify the analyst who did the work so that any problems can be discussed and corrected.

5.5.2 Once the auditor is satisfied that the data are acceptable, the work is submitted to a manager or supervisor for final approval of the data and for acceptance or rejection of the material that was tested.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Laboratory Failure Investigations**	NUMBER: **033**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define the requirements for dealing with failing (out-of-specification) laboratory results.

2.0 SCOPE:

2.1 All laboratory results that impact upon acceptance or rejection of finished products or raw materials.

3.0 RESPONSIBILITY:

3.1 Laboratory managers, supervisors, and auditors.

4.0 FREQUENCY:

4.1 Upon completion of analytical work, before final approval.

5.0 PROCEDURE:

5.1 Where results of manufacturing steps deviate from parameters specified in manufacturing formulas or SOPs, as evidenced by a failing laboratory result, an informal laboratory investigation will be conducted to determine why the deviation occurred and whether the source of the deviation was laboratory or manufacturing related.

5.2 In the case of analytical results, both chemical and microbiological data that are out of specification will be verified through a process of retesting and/or resampling.

5.3 If results are subsequently changed, the new results must be backed up by appropriate laboratory data. Where additional steps are performed beyond those specified in a written SOP, the additional steps will be clearly documented.

5.4 Specifically, if one (1) out-of-specification result is obtained, an informal laboratory investigation will be conducted and documented via a checklist.

5.5 The analyst who performed the test must report the occurrence to his or her supervisor and two (2) analysts plus a supervisor must conduct an informal laboratory investigation, inspecting the notebook/worksheet containing the out-of-specification result, discussing the testing procedure with the analyst who performed the work, along with any required calculations, and examining the instrument or instruments used.

5.6 The checklist and results of the investigation will be preserved in a "failure investigation report" and stored with the raw analytical data in a laboratory notebook or worksheet.

5.7 In the case where the out of specification result can be definitively explained, simple retesting can be used to invalidate the original result. Note: Averaging of an in-spec result with an out-of-spec result to produce an in-spec average is *never permitted.*

5.8 In the case where the out-of-specification result is unexplained, a retest from the original sample container must be performed plus a retest of a different sample container, resampling if necessary, to obtain the new sample. If passing results are obtained on both retests, then the original failing result is invalidated and may be discarded. If two (2) unexplained failing results are obtained, the batch is rejected. Retesting must be done with new standard weighings and new batches of reagents. The retests must be performed by a second analyst.

5.9 In all cases, investigations will be completed and a written investigation report issued within 20 business days of a deviation (failure). Investigation reports that include steps taken, raw data, findings, and conclusions will become a permanent part of the batch record for the product under investigation, and in the case of raw materials, a permanent part of the raw material testing report.

5.10 For batches that are rejected, the failure is either a process or non-process or operator error which must be subjected to a formal failure investigation by manufacturing management.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

LABORATORY INVESTIGATION CHECKLIST AND REPORT

Product: _____

Batch: _____

Name of analyst who reported occurrence: _____

Reported to: _____ Title: _____

Investigating supervisor: _____

Investigating analyst: _____

Notebooks/worksheets inspected? (Y/N): _____

Discussion of test procedure? (Y/N): _____

Examination of calculations? (Y/N): _____

Examination of instruments? (Y/N): _____

FINDINGS AND RECOMMENDATIONS:

Signatures and Date: _____ _____

_____ _____

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Reserve Samples**	NUMBER: **034**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 1
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define the requirements for taking, storing, and discarding reserve samples.

2.0 SCOPE:

2.1 All raw materials and finished products.

3.0 RESPONSIBILITY:

3.1 Laboratory management.

4.0 FREQUENCY:

4.1 Upon completion of analytical work, after final approval.

5.0 PROCEDURE:

5.1 For each lot or batch of raw material or finished product that is tested by the laboratory, or released for commercial distribution, a reserve sample must be taken.

5.2 The quantity of reserve sample must be at least twice that needed to perform all required testing on the sample.

5.3 Reserve samples must be stored under conditions of temperature and humidity that correspond to that recommended for commercial quantities of the material.

5.4 Reserve samples must be retained for at least one year beyond the expiration date of the product lot or batch that it represents. In the case of raw materials, the retention time is at least one year beyond the expiration data of the product for which the raw material was used. If a raw material went into more than one product, then that raw material reserve sample should be retained for one year beyond the shelf life of the product that has the longest shelf life.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Raw Material Testing and Vendor Certification**	NUMBER: **035**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a scheme for laboratory testing of raw materials used in pharmaceutical applications.

2.0 SCOPE:

2.1 All pharmaceutical raw materials.

3.0 RESPONSIBILITY:

3.1 Laboratory management.

4.0 FREQUENCY:

4.1 As raw materials are received and tested.

5.0 PROCEDURE:

5.1 Protocol for testing applies separately to each raw material vendor. Refer to individual testing monographs for analytical requirements.

5.2 Active Drug Substances

5.2.1 For fewer than 10 lots per year, if at least one (1) lot received each calendar year from a vendor meets all specification requirements as established by full monograph testing, then for that calendar year, and as long as a certificate of analysis has been received from the vendor showing full monograph testing, the only in-house testing required for release is at least one *identification* test and *appearance*.

5.2.2 For 10 or more lots a year, step 5.2.1 should be applied to every tenth lot of raw material received from each vendor.

5.2.3 Assay, although not required, is recommended as an internal assurance of purity for each lot of raw material received.

5.2 Inactive Materials (Excipients)

5.2.1 In-house testing may be limited to one identification test and appearance, as long as a certificate of analysis has been received from the vendor showing full monograph testing for all items defined by material specifications.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Equipment Identification**	NUMBER: **036**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 2
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define a system for identification of laboratory instrumentation and apparatus.

2.0 SCOPE:

2.1 All Laboratory Equipment—Makes for easy referencing of equipment used for analytical work, either by equipment or system number

3.0 RESPONSIBILITY:

3.1 Laboratory management.

4.0 FREQUENCY:

4.1 As instrumentation is received, modified, or discarded.

5.0 PROCEDURE:

5.1 A master inventory log should be kept of all laboratory equipment that includes equipment name, brand, model number, date received, and serial number.

5.2 For self-contained equipment, such as pH meters, ovens and balances, a label should be affixed to that equipment that identifies it by instrument and number, such as "Balance #1" or "Oven #2." The instrument label and the identification of that instrument in the master inventory log must agree.

5.3 For equipment such as HPLCs, a label should be affixed to a principal component of the system (pump for example), identifying all of the components that make up the HPLC instrument as a SYSTEM. For example, if there were four (4) HPLC systems, each consisting of multiple components such as pumps, detectors, and integrators, they would be labelled HPLC SYSTEM #1 through #4 respectively.

5.4 When dealing with systems, the components of the system must be identified as those making up that particular system. The system number must be documented so that any particular system, such as SYSTEM #1, has each component specified by name, brand, model number, and serial number. An easy way to do this is to list individual components as separate pieces of equipment in the master inventory log, and then to identify the components of a system by serial number only. The serial numbers can be easily cross-matched between systems and the master inventory log.

5.5 New equipment must added to the master log and labeled upon receipt.

5.6 Old equipment that has been discarded must be removed from active status in the master inventory log and its labels destroyed.

5.7 For systems such as HPLCs, a change in one or more components, such as switching pumps or detectors, must be documented to reflect the current component makeup of that particular system.

5.8 Associated equipment such as HPLC and GC columns or pH electrodes should have their own use logs that track usage history, including hours in service and what analyses were run using a particular piece of associated equipment. The associated equipment log should also contain any record of maintenance performed on such equipment such as column or electrode reconditioning.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Audit of Outside Laboratories and Internal Laboratory Audits**	NUMBER: **037**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 3
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To describe the principal components of a laboratory audit.

2.0 SCOPE:

2.1 GMP/GLP audit of all contract laboratories used to perform analytical work, either chemical or microbiological, and internal audit of all laboratories that perform analytical work, either chemical or microbiological.

3.0 RESPONSIBILITY:

3.1 Laboratory management, Quality Assurance

4.0 FREQUENCY:

4.1 Yearly

5.0 PROCEDURE:

5.1 Chemistry and Microbiology

5.1.1 Personnel

Determine whether or not chemists have the training, education, and/or experience necessary to perform chemical analyses in a pharmaceutical laboratory environment. Similarly, determine whether or not microbiologists have the training, education, and/or experience necessary to perform microbiological analyses in a pharmaceutical laboratory environment. See if there is a training program in place, and check to see that analysts have been properly trained in the work that they are doing.

5.2 Standard Operating Procedures

Determine whether or not standard operating procedures are in place for all operations and if they are being followed. This applies to all SOPs, including analytical methods, specifications, and testing protocols (control schedules).

5.1.3 Instruments and Equipment

Determine whether or not there is a calibration program in place for all analytical equipment and instrumentation, and whether or not equipment is stickered with current calibration stickers and properly identified by instrument or system number.

5.1.4 Standards and Reagents

Determine if there are USP and/or house standards available for all product analyses as well as a system for reviewing expiration and replacement of standards. In addition, check to see if there is a program for labelling and outdating of volumetric and test solutions as well as dry chemical reagents.

5.1.5 Stability

Determine whether or not stability chamber controls are adequate, and if the stability testing program is up to date, and if suitable and continuous monitoring of stability chambers is performed with calibrated temperature and humidity monitoring devices. Check to see that the stability chambers are serviced and calibrated on a regular basis.

5.1.6 Notebooks and Worksheets and Audit Trail to Raw Data

Check to see whether or not notebook and or worksheet management practices are adequate. Evaluate the laboratory's ability to trace raw data in notebooks and worksheets from final result sheets, and if ancillary documentation such as chromatograms and spectra are easily located for any particular analysis. Determine the efficacy of audit trails by selecting five (5) result sheets at random and tracking back to raw data and ancillary documents, using only the information contained in the laboratory's documentation. See if there is a system in place to log samples into the laboratory and to track the flow of work as it proceeds.

5.1.7 Failure Investigations

Make sure that there is a written policy for handling of out-of-spec laboratory data. This should include an informal laboratory investigation and a mechanism for retesting, resampling, and proper disposition of final data.

5.1.8 Housekeeping and Safety

Look carefully at housekeeping practices. The laboratory should be clean and uncluttered, and there should be adequate space for analysts to perform their work. Check to see if there is a program in place for safety training and monitoring and that the laboratory is in compliance with the OSHA laboratory standard.

5.1.9 Analytical Methods and Validations

Determine whether or not analytical methods are adequate to support work submitted to the laboratory. Check to see if methods are validated, and that if they are used for stability work, they are stability indicating. Make sure that compendial analyses are being done by the current compendial methodology or methodology for which equivalence to compendial methods has been demonstrated by laboratory studies.

5.1.10 Management Systems

Determine whether or not there is adequate span of authority for QC management review, and release and rejection of materials tested by the laboratory.

5.1.11 Microbiology Only

A micro audit for GMP compliance needs to address such issues as review of lab logs, review of SOPs, autoclave validation, pressure and temperature control, retest policies, use of positive and negative controls, media validations, and growth promotion tests. This is best performed by an experienced microbiologist who is familiar with FDA micro inspection guidelines.

5.1.12 Quality Assurance

Determine what quality assurance measures, if any, are in place to guarantee the efficacy of data that are published, such as internal audits, use of control samples, training, data review, and use of statistical quality control techniques.

5.2 Documentation

5.2.1 Prepare an audit report that lists any GMP or GLP deficiencies that were noted during the audit and suggestions for correction of those deficiencies.

5.2.2 Submit the report to the Laboratory Director.

5.2.3 Request a response that details corrective action plans, if any, to rectify the deficiencies noted during the audit.

5.2.4 During the next audit, start by determining whether or not previous deficiencies have been corrected before beginning the formal yearly audit.

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

ATTACHMENT

CHAPTER 7: QUALITY ASSURANCE

Components of the Sample Compliance Program for Pharmaceutical and Chemistry Laboratories

I. Instrument and Equipment Calibration
II. Standards and Reagents
III. Standard Operating Procedures (SOPs)
IV. Laboratory Logs
V. Failure Investigations
VI. Stability
VII. Microbiology
VIII. Analytical Methods and Methods Validation
IX. Notebooks
X. Chromatograms and Spectra
XI. Training
XII. Management Systems/QC

I. Instrument and Equipment Calibration

A. High Pressure Liquid Chromatograph (HPLCs)
B. Gas Chromatograph
C. Infrared Spectrophotometer
D. UV/Visible Spectrophotometer
E. Dissolution Apparatus
F. pH Meters
G. Ovens and Furnaces
H. Karl Fisher Apparatus
I. Analytical Balances and Top-Loading Balances
J. Stability Chambers
K. Thermometers
L. Data Systems

CALIBRATION

SOP required

Title: Calibration of HPLC Systems

Frequency: Every six months minimum, quarterly for a high-volume laboratory, and after service is performed on a component of the system.

Responsibility: Laboratory director

Components: System components need individual check of performance. Pumps should have flow checked under load (through a column) at several flow rates that bracket flows used for analytical work. This is accomplished via graduate cylinder and stopwatch. Injectors should have injection precision measured over a range of injection volumes that bracket those used for analytical work. Detectors should be given a linearity check at several wavelengths, preferably those used for major product analysis.

Documentation: If calibration passes, place a sticker on the instrument showing date calibrated and the date that calibration expires. If calibration fails, place an out-of-service sticker on the unit until the system is repaired and passes a calibration check. Document the calibration and any repairs in a calibration notebook reserved for HPLC systems.

MAINTENANCE

SOP required

Title: Maintenance of HPLC Systems

Frequency: As described

Responsibility: Laboratory director

Components: On a yearly basis, instrument vendor should provide a complete preventative maintenance and certification service. On a quarterly basis, user should change pump seals, and check lamp life and autosampler components for wear, replacing parts as needed.

Documentation: Record all service in an HPLC maintenance notebook. Maintenance and calibration notebooks can be combined.

GENERAL

1. Each HPLC system should have a system ID number.
2. For each system, there should be a listing of the components of that system, which includes the serial numbers for each component of the system.
3. When documenting HPLC assays, the ID number of the system used for that particular analysis should be referenced.

CALIBRATION

SOP Required

Title: Calibration of Gas Chromatographs

Frequency: Every six months

Responsibility: Laboratory director

Components: System components need individual check of performance. Flow controllers should be checked for accuracy of gas flow at several flow rates that bracket flows used for analytical work. This is accomplished via a bubble meter and stopwatch. If an autoinjector is used, then the injector should have injection precision measured over a range of injection volumes that bracket those used for analytical work. Detectors should be given a linearity check at several settings. For example, a flame ionization detector should be tested at several ranges and a thermal conductivity detector tested over several bridge currents.

Documentation: If calibration passes, place a sticker on the instrument showing date calibrated and date that calibration expires. If calibration fails, place an out-of-service sticker on unit until the system is repaired and passes a calibration check. Document the calibration and any repairs in a calibration notebook reserved for GC systems.

MAINTENANCE

SOP Required

Title: Maintenance of Gas Chromatography Systems

Frequency: As described

Responsibility: Laboratory director

Components: On a yearly basis, instrument vendor should provide a complete preventative maintenance and certification service. This should include verification of the accuracy of all temperature zones. On a daily basis, user should check gas supply, flow rates, temperatures, and replacement of septa.

Documentation: Record all service in a GC maintenance notebook. Maintenance and calibration notebooks can be combined.

GENERAL

1. Each GC system should have a system ID number.
2. For each system, there should be a listing of the components of that system, which includes the serial numbers for each component of the system.
3. When documenting GC assays, the ID number of the system used for that particular analysis should be referenced.

CALIBRATION AND MAINTENANCE

SOP Required

Title: Calibration and Maintenance of Infrared Spectrophotometer

Frequency: Monthly calibration/yearly for maintenance

Responsibility: Laboratory director

Components: The infrared spectrophotometer should be calibrated by scanning the spectra of a polystyrene film. When compared to a standard spectra for polystyrene (from the literature), the wavelengths of the peaks obtained by in-house scan should match those of the reference spectrum. On a yearly basis, a preventative maintenance call by the instrument manufacturer should be performed to certify that the instrument meets factory specs and to make any needed adjustments.

Documentation: If the polystyrene scan is suitable versus the standard spectrum, then sticker the IR as calibrated to include the date calibrated and the calibration expiration date. If the polystyrene scan is not suitable versus the standard spectrum, then label the unit out of service until it is repaired and properly calibrated. Document all maintenance and calibration done in an IR Maintenance and Calibration notebook.

GENERAL

1. Run IR spectra of samples versus in-house standard spectra.
2. Maintain a library of standard spectra.
3. Once a standard has been run in-house, samples can be compared to it until a new reference lot of standard is issued.
4. Follow USP guidance, if available, for sample preparation.

CALIBRATION AND MAINTENANCE

SOP Required

Title: Calibration and Maintenance of UV/Visible Spectrophotometer

Frequency: Every six months for calibration/ yearly for maintenance

Responsibility: Laboratory director

Components: The UV/Visible spectrophotometer is calibrated via a wavelength accuracy check. Since this instrument is ordinarily used primarily as an identification tool, it is generally sufficient to calibrate via a wavelength check. This is accomplished by scanning a holmium oxide reference glass from 700 to 200 nanometers. The scanned wavelengths should match the standard wavelengths for holmium oxide within 0.5 nanometers. If the instrument is used for quantitative work, then it is necessary to perform a detector linearity check as well.

Documentation: If the holmium oxide scan and/or linearity check is suitable, then sticker the UV/VIS as calibrated to include the date calibrated and the calibration expiration date. If the calibration fails (out of spec), then label the unit out of service until it is repaired and properly calibrated. Document all maintenance and calibration in a UV/VIS Maintenance and Calibration notebook.

GENERAL

1. Run UV/VIS spectra of samples versus in-house standard spectra.
2. Run a fresh standard scan for each sample.
3. Follow USP guidance, if available, for sample preparation.

CALIBRATION AND MAINTENANCE

SOP Required

Title: Calibration and Maintenance of Dissolution Apparatus

Frequency: Daily or when used for maintenance/every six months for calibration

Responsibility: Laboratory director

Components: Daily maintenance—Before each use, check level of unit, water level, warble, distance of shaft from sides of vessel, space under paddle or basket, and water bath temperature. Check condition of paddles and/or baskets and be sure that the table upon which the unit is seated is free of vibration. Six month calibration—Calibrate with USP prednisone calibrator tablets. Check accuracy of shaft rotation as well as level of unit and centering of paddles or baskets.

Documentation: If the prednisone calibration is suitable, then sticker the dissolution apparatus as calibrated to include the date calibrated and the calibration expiration date. If the calibration fails (out of spec), then label the unit out of service until it is repaired and properly calibrated. Document all maintenance and calibration done in a Dissolution Maintenance and Calibration notebook. Also, document any abnormalities found in the daily checks.

CALIBRATION

SOP Required

Title: Calibration of pH Meters

Frequency: Daily or when in use

Responsibility: Laboratory director

Components: For two-point calibration meters (most common), set the slope control to 100%. Adjust the temperature control to the temperature of the buffer and solutions to be measured. Measure the pH of a standard pH 7.0 buffer. Use the calibrate control of the meter, if necessary, to adjust the displayed reading to 7.00 pH units. For measurements below pH 7.0, measure the reading of a pH 4.0 buffer solution. Adjust the slope control to set the meter display to 4.00. For measurements above pH 7.0, measure the reading of a pH 10.0 buffer solution, adjusting the slope control to achieve a display reading of 10.00.

Documentation: Record, in a pH meter logbook, the lot number of buffers used, readings obtained for the buffer solutions, and any slope correction that was made to achieve calibration. If the meter cannot be calibrated (slope control cannot produce buffer value), check the electrode and the buffers. Do not use for measurement of sample until a suitable calibration has been performed.

GENERAL

1. Make sure that there is adequate filling solution in electrodes.
2. Keep electrodes immersed in buffer or tap water when not in use.
3. Be careful not to use buffers that are past their expiration dates.
4. For single-point calibration type pH meters, follow manufacturer's instruction for calibration.

CALIBRATION AND MAINTENANCE

OVENS

SOP required

Title: Calibration of Ovens

Frequency: Yearly

Responsibility: Laboratory director

Components: Outside vendor does calibration of ovens to assure that temperatures are accurate and linear. Daily control is achieved through use of a calibrated thermometer.

Documentation: Preserve outside vendor calibration report for inspection.

FURNACES

SOP required

Title: Calibration of Furnaces

Frequency: Yearly

Responsibility: Laboratory director

Components: Outside vendor does calibration of furnaces to assure that temperatures are accurate and linear.

Documentation: Preserve outside vendor calibration report for inspection.

CALIBRATION

SOP Required

Title: Calibration of Karl Fisher Apparatus

Frequency: Daily or when in use

Responsibility: Laboratory director

Components: Methanol or other titration solvent is blanked out with Karl Fisher reagent (Karl Fisher reagent or Hydranal™). Water or sodium tartrate is used to standardize the KF reagent by computing milligrams of water consumed by each milliliter of KF reagent.

Documentation: The mg/mL of water (water factor) for each calibration (standardization) should be recorded in a Karl Fisher calibration book.

GENERAL

1. If a manual Class-A buret is used, then the KF standardization is adequate.

2. If an automatic buret system is employed, such as a Brinkmann or Mettler unit, then the buret module must be calibrated by weighing incremental dispensing of water to insure buret accuracy.

CALIBRATION

ANALYTICAL BALANCES

SOP Needed

Title: Calibration of Analytical Balances

Frequency: Daily or when in use

Responsibility: Laboratory director

Components: Using ASTM Class 1 weights (having traceable certificates of calibration), balances should be checked daily, using weights that bracket the range of weights to be used in routine analytical work. The ASTM Class 1 weights need to be sent out for recalibration on a yearly basis.

Documentation: The observed weights, actual weights (from certificate), and the difference should be recorded for each weight checked. If the balance is out of tolerance, put it out of service until it is repaired. Record the calibration in a Balance Calibration notebook.

MAINTENANCE

ANALYTICAL AND TOP-LOADING BALANCES

SOP Needed

Title: Maintenance of Laboratory Balances

Frequency: Every six months

Responsibility: Laboratory director

Components: An outside balance calibration service should service and certify the accuracy and linearity of the balances as per the above frequency.

Documentation: Outside vendor should sticker balances with calibration date and calibration expiration date.

CALIBRATION

SOP Required

Title: Calibration of Stability Chambers

Frequency: Every six months/daily monitoring

Responsibility: Quality Control manager

Components: Controlled room temperature stability rooms should be kept at 25–30°C at a relative humidity of about 60%. The room should be monitored continuously with chart recorders and the charts preserved as a permanent record of temperature and humidity. Recorders should be placed at several points throughout the room to assure even temperature distribution, and the recorders should be calibrated every six months by an outside calibration service. In addition, the room controls themselves should be serviced every six months by an outside calibration service. Accelerated chambers need to be kept at 40°C and 75% relative humidity. Service and monitoring requirements are the same as those for room temperature units.

Documentation: Temperature and humidity charts should be saved and logged into a stability chamber notebook. The calibration reports from the outside calibration service should also be preserved in such a notebook.

CALIBRATION

SOP Required

Title: Calibration of Thermometers

Frequency: Yearly

Responsibility: Laboratory director

Components: Laboratory thermometers should be sent out for calibration yearly. The calibration should be a three-point calibration for each thermometer. The outside vendor should supply a calibration certificate that includes such data as actual temperature versus measured temperature, correction, if any, at each point of each thermometer calibrated, reference to standard thermometers used, and evidence of their traceability to NIST thermometers. Alternately, in-house calibration could be performed versus an NIST traceable thermometer set. Thermometers should be numbered for reference purposes and cataloged by number.

Documentation: Calibration certificates or calibration data for each thermometer should be preserved in a calibration notebook.

CALIBRATION

SOP Required

Title: Calibration of Chromatography Data Systems

Frequency: One time only

Responsibility: Laboratory director

Components: An outside calibration service should validate the data system by using an NIST traceable signal generator to inject calibrated signals into the data system input and demonstrate that the area units per microvolt are as rated by the data system manufacturer. In addition, in-house verification of data system calculations by manual cross-check should be performed.

Documentation: Record the one-time calibration data in a hardbound notebook.

II. Standards and Reagents

A. USP, House, and Purchased Standards
B. Solutions and Dry Reagents

USP STANDARDS

USP Standards are required for all compendial monograph work. These can be purchased from the US Pharmacopeial Convention. USP standards should be stored under recommended storage conditions. Only the current regulatory lot should be used. Current lot numbers are listed in the Pharmacopeial Forum or in the USP standards catalog.

HOUSE STANDARDS

In lieu of USP standards, house standards assayed versus USP standards may be used. House standards should be recertified every six months versus a current regulatory lot of USP standard.

SOP Required

Title: Use of Analytical Standards

Frequency: Per use

Responsibility: Laboratory director

Components: As described above

Documentation: A log of USP standards should be kept by name and lot number. A periodic inventory should be taken and documented to assure that only current lots are in the system. Results of house standard certification should be recorded in a house-standards notebook.

PURCHASED STDs

When it is not possible to obtain USP or house standards or some other certified chemically pure standards such as BP standards, purchased prepared standards may be used.

SOP Required

Title: Use/Control of Purchased/Prepared Standards

Frequency: Per use

Responsibility: Laboratory director

Components: As described above

Documentation: A log of purchased standards should be kept by name and lot number. A periodic inventory should be taken and documented to assure that only current lots are in the system. Results of internal standard control and audit of vendor should be recorded.

VOLUMETRIC SOLUTIONS

SOP Required

Title: Preparation and Standardization of Volumetric Test Solutions (TS)

Frequency: As needed

Responsibility: Laboratory director

Components: Volumetric test solutions should be prepared and standardized as per the USP. Even store-bought solutions need in-house standardization. Volumetric TS need to be given a shelf life, at which time restandardization is required.

Documentation: The preparation and standardization should be recorded in a Volumetric TS notebook. All raw data, including lot number of primary standard, titration values, and calculations must be shown. The volumetric solutions themselves should be stickered to show solution name, concentration, date standardized, expiration date, and notebook reference to standardization notebook.

TEST SOLUTIONS AND INDICATORS

Solutions should be labeled with name and expiration date. Buffer solutions may be store-bought as long as they are not kept beyond their listed expiration dates.

DRY REAGENTS

Dry chemicals should be labeled with a receiving date and expiration date (usually one year), and stored under appropriate conditions.

GENERAL

Periodic inventories should be taken on all of the above to avoid having expired materials in service.

III. Standard Operating Procedures

The following is a list of minimum recommended SOPs for the laboratory:

1. Creation of SOPs and change control
2. Sampling, receiving, testing, and disposition of raw materials
3. Sampling, receiving, testing, and disposition of in-process materials
4. Sampling, receiving, testing, and disposition of finished products
5. Analytical methods validation
6. Use of analytical standards
7. Preparation and standardization of volumetric solutions
8. Analytical method monographs
9. Specification sheets
10. Calibration of HPLCs
11. Calibration of GCs
12. Calibration of IR spectrophotometer
13. Calibration of UV/VIS spectrophotometer
14. Calibration of dissolution apparatus
15. Calibration of pH meters
16. Calibration of ovens
17. Calibration of furnaces
18. Calibration of Karl Fisher apparatus
19. Calibration of balances
20. Calibration of stability chambers
21. Calibration of thermometers
22. Validation of chromatography data systems
23. Laboratory logs
24. Handling of test solutions, indicator solutions, buffer solutions, and dry chemicals
25. Reserve samples and records
26. Failure investigations
27. Standard practices for chromatography
28. Storage and expiration of stock standard solutions
29. Shelf life determination of stock standards
30. Laboratory training program
31. Notebook maintenance
32. Management span of authority
33. Audit of outside laboratories
34. Documentation practices

IV. Laboratory Logs

Samples coming into the laboratory should be logged into the laboratory system via a formal lab log book—one book for raw materials and one for intermediates and finished products. The entries would include lot number, date received, sample type, packaging, and date released. This permits a sequential list of sample to be generated that is easy to maintain and use in locating any particular sample and its status.

V. Failure Investigations

As a result of a United States Federal Court decision, there is a very specific requirement for treating out-of-spec (OOS) data generated by the laboratory in a pharmaceutical operation.

SOP Required

Title: Failure Investigations

Frequency: As needed

Responsibility: Laboratory director

Components: As per a U.S. Federal Court decision, if an OOS is generated, an informal lab investigation must be conducted where the analyst is questioned by his or her supervisor and by another chemist as to the methodology, instrumentation, reagents, etc. If the OOS is explainable, then a simple retest can overcome the original result. If the OOS is unexplained, then a second analyst must repeat the analysis using fresh standards and reagents on the original sample as well as on a resample. If both results pass, the OOS can be rejected. If a second unexplained result is generated, then testing stops and the batch is "dead."

Documentation: A one-page checklist is adequate for recording the informal lab investigation. Such a checklist is show on the following page.

Failure Investigations

LABORATORY INVESTIGATION CHECKLIST AND REPORT

Product: _____

Batch: _____

Name of analyst who reported occurrence: _____

Reported to: _____ Title: _____

Investigating supervisor: _____

Investigating analyst: _____

Notebooks/worksheets inspected? (Y/N): _____

Discussion of test procedure? (Y/N): _____

Examination of calculations? (Y/N): _____

Examination of instruments? (Y/N): _____

FINDINGS AND RECOMMENDATIONS:

Signatures & Date: _____ _____

_____ _____

VI. Stability

One sample of each different container for one lot of each product must be placed on room temperature stability each year. The normal stability stations are initial, 3, 6, 9, and 12 months minimum, plus 18, 24, 36, 48, and 60 months, depending on how long a shelf life is needed. For OTC, non-ANDA products the testing schedule is initial, 6 months, 12 months, 18 months, and 24 months, then once a year to desired shelf life. The lab must test each station within one month of the due date for RT (room temperature) samples, and within one week for accelerated, using stability indicating methodology that has been validated through use of forced degradation studies. Stability chambers must be calibrated and monitored to assure that proper temperature and humidity conditions are maintained.

VII. Microbiology

Outside microbiology labs should be audited on a yearly basis to assure conformance with FDA micro lab guidelines. A micro audit for GMP compliance needs to address such issues as review of lab logs, review of SOPs, autoclave validation, pressure and temperature control, retest policies, use of positive and negative controls, media validations, and growth promotion tests. This is best performed by an experienced microbiologist who is familiar with FDA micro inspection guidelines.

VIII. Analytical Methods and Methods Validation

ANALYTICAL METHODS

Each analytical procedure should have an in-house written monograph in the form of an SOP. This includes compendial methods, which should be paraphrased using in-house monographs.

SOP Required

Title: Name of Assay or Test

Frequency: Per use

Responsibility: Laboratory director

Components: Monograph should contain a list of reagents and equipment, standard preparation, sample preparation, procedure, and calculations. In addition, if the method is an HPLC or GC method it should include a sample chromatogram that establishes typical peak shapes and retention times.

Documentation: All raw data generated by use of a monograph should be stored in hardbound notebooks or prenumbered worksheets. Chromatograms can be kept in a separate looseleaf notebook and referenced in the primary hardbound notebook or worksheet.

METHODS VALIDATION

SOP Required

Title: Validation of Analytical Methods

Frequency: As needed

Responsibility: Laboratory director

Components: Method validation should deal with performance parameters needed to demonstrate that the method is suitable for its intended use. Stability Indicating Aspects—Stability indicating studies demonstrate baseline separation between principal peaks and degradation products after the sample is subjected to forced degradation studies. This requires the use of diode array detector technology for UV analyses. Selectivity—Degree of bias of test results obtained by analysis of samples containing impurities such as placebo ingredients versus sample without added substances. Linearity and Range—The method must be able to produce results that are proportional to analyte in sample solutions, within the range of 50–150% of the working standard concentration. Accuracy and Recovery—Accuracy is the closeness of test results obtained by the method to the true value. It is expressed as percent recovery of known, added amounts of analyte and is a measure of method exactness. Assay Precision—Degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample and is usually expressed as relative standard deviation (RSD) of the percent result.

Documentation: All raw data are preserved as described under analytical methods.

IX. Notebooks

All raw data such as weights, titration values, or any other observed data should be recorded in a hardbound notebook or on prenumbered worksheets. In the case of notebooks, there should be an SOP that describes how notebooks are issued, controlled, and archived. In the case of prenumbered worksheets, there should be an SOP that describes the system for issuance, sign off, destruction, and preservation of such worksheets, as well as a mechanism by which to prevent unauthorized issuance or duplication of prenumbered worksheets. Notebook pages or worksheet pages should contain date, project name, method used, and all raw data such as weights, lot numbers of standards, and references to preparation of solutions used such as volumetric test solutions. Each page should be signed by the author and audited by a witness who countersigns and dates each page. Errors are corrected by drawing a single line through the error and rewriting the new entry above the old one. All changes must be initialed and dated, and where the reason for the change is not obvious, a written explanation should accompany the change.

X. Chromatograms and Spectra

The FDA has adopted a philosophy when inspecting QC laboratories that "chromatograms tell the tale." The quality of chromatograms generated by HPLC and GC assays is critical to good raw data integrity. Peak shapes should be symmetrical, and all work such as tailing factor, resolution, theoretical plates, capacity factor, and system suitability should be shown on the chromatograms. The chromatograms should show standards and samples run in a sequence that makes sense for the time frame of the analysis. For example, samples should not be run 10 hours after standards. Chromatograms should be easily traceable from notebook references. Spectra from IR and UV/VIS scans should be preserved and should be easily traceable from notebook references. Original spectra should be saved, not copies.

XI. Training

All employees are required to receive GMP training upon employment. In addition, each employee is required to be retrained yearly on those operations applicable to his or her particular job. In the laboratory, training includes safety, lab SOPs, analytical methods, and QC procedures such as sampling, treatment of data (good and bad), and releasing of samples. This training should be ongoing and must be documented.

XII. Management Systems

There should be SOPs in place that define management span of authority in terms of releasing and rejecting materials. QC needs to able to perform such tasks autonomously, without influence from manufacturing. In addition, there needs to be adequate change control mechanisms, as well as procedures for reviewing batch deviations and analytical data and for assuring that each employee has the necessary training, education, and experience needed to perform his or her job.

CHAPTER

8

SPACE System of Laboratory Management: Safety

Chapters three through seven, "Tools of the Trade," described the 14 tools needed for comprehensive management of the analytical laboratory. This chapter, by contrast, is geared towards a cookbook or flow-sheet approach of how to do it, because it presents material in a step-by-step sequence as components of a complete management plan for the analytical laboratory that is built upon the "Tools of the Trade."

What is the SPACE system of laboratory management? It is a five (5) component system of laboratory management defined by the SPACE acronym:

S AFETY
P RODUCTIVITY
A CCURACY
C REDIBILITY
E DUCATION

The safety component of the SPACE system consists of safety issues discussed in section 3.5 of chapter 3, but mainly, it deals with the OSHA Laboratory Standard as a safety tool and as a safety performance standard required by law. Productivity is achieved by structured use of tools of the trade and by the use of control samples. Accuracy is guaranteed through statistical quality control

coupled with application of the quality assurance techniques already discussed. Credibility is developed and maintained through the use of proper documentation, control charts, and a program of blind controls. *Education* addresses the means of administering training, employee competence evaluations, and professional growth, plus training documentation and reporting.

8.1 SAFETY

8.1.1 Internal Safety Program

Recommended actions for an internal laboratory program are as follows:

1. Develop a written safety program that spells out safety requirements such as
   a. Safety committee membership
   b. Frequency of safety meetings
   c. Frequency of safety inspections
   d. Frequency of safety training
   e. How the laboratory is to comply with OSHA
   f. Documentation of above items
2. Develop management/worker safety committee.
3. Hold safety meetings monthly. Let a different employee speak on safety topics each month.
4. Hold laboratory safety inspections monthly. Issue deficiency report, and require correction by the following month, except for critical items, which should be corrected immediately.
5. Hold safety training for all new employees prior to starting any lab work.
6. Create an environment where every employee is a safety inspector. Rotate members of the safety committee so that everyone has an active participatory role in safety planning and implementation.

Components of the above internal safety program are presented as guidelines which will serve to enhance and perpetuate safety awareness. However, it is up to management and workers alike to develop the specifics of any program and to monitor that program regularly.

While safety awareness and a good internal safety program are important, each and every analytical laboratory must also be concerned with safety compliance.

8.1.2 OSHA Laboratory Standard

On January 31, 1990, the Occupational Health and Safety Administration (OSHA) put into effect the "Occupational Exposures to Hazardous Chemicals in Laboratories," also known as the "OSHA Laboratory Standard." The purpose of the Standard is to protect laboratory employees from adverse effects of hazardous chemicals with which they may come into contact in the workplace. The

OSHA Laboratory Standard is cited in the United States Code of Federal Regulations, Title 29, Part 1910.

This regulation (standard) applies only where the use of hazardous chemicals meets OSHA's definition of "laboratory use of hazardous chemicals" and "laboratory scale" as defined in the Standard.

The OSHA Laboratory Standard is a performance standard, which means that instead of telling you exactly what to do, it tells you what you must accomplish, allowing room for creativity and innovation in complying with the Standard. The OSHA Laboratory Standard went into effect on May 1, 1990, requiring all employers to develop and implement a written chemical hygiene plan by no later than January 31, 1991.

The purpose and intent of the Standard is to protect employees from chemical hazards that they may encounter in their workplace. For the purpose of the Standard, a hazardous chemical is defined as follows:

> A chemical for which there is statistically significant evidence, based on at least one study conducted in accordance with established scientific principles, that acute or chronic health effects may occur in exposed employees. The term "Health Hazard" includes chemicals which are carcinogens, toxic or highly toxic agents, reproductive toxins, irritants, corrosives, sensitizers, hepatotoxins, nephrotoxins, neurotoxins, agents which act upon hematopoietic systems and agents which damage the lungs, skin, eyes or mucous membranes.

Remember, the OSHA Laboratory Standard is a performance standard that states what must be accomplished. How can one be sure that proper actions are taken to assure compliance with the Standard? There are two principal compliance tools that must be used to achieve the intent of the Standard. The first step is to prepare a written chemical hygiene plan.

The written chemical hygiene plan must accomplish two things: protect employees from health hazards associated with hazardous chemicals in the workplace (laboratories) and keep exposures below the limits specified in the Standard. In order to accomplish these two things, the written plan must include many of the elements defined in the Standard such as the following:

1. Standard safety and health related operating procedures that must be followed when laboratory work involves the use of hazardous chemicals.
2. Criteria that will be used to determine and implement control measures needed to reduce employee exposure to hazardous chemicals, such as engineering controls, use of personal protective equipment, and personal hygiene practices.
3. SOPs to determine fume hoods and other personal protective equipment are operating properly, and specific actions to be taken to ensure that this equipment will function properly and provide adequate performance at all times.
4. Provisions to make sure that employees will be given information and training specified by the Standard in its section on "Employee Information and Training."

5. Definitions of the circumstances under which a particular laboratory operation, procedure, or activity will require prior approval by the employer.
6. Provisions for medical consultations and examinations in accordance with the section of the Standard "Medical Consultation and Medical Examinations."
7. Designation of personnel responsible for implementing the Chemical Hygiene Plan, including assignment of a "Chemical Hygiene Officer" and establishment of a "Chemical Hygiene Committee."
8. Provisions for additional employee protection when working with particularly hazardous substances, such as select carcinogens, reproductive toxins, or substances having a high degree of acute toxicity.

When working with these substances, particular attention must be given, where appropriate, to having a designated work area for these substances, use of containment devices (fume hoods, glove boxes), procedures for safe removal, and decontamination procedures.

The OSHA Laboratory Standard requires review of the written chemical hygiene plan at least annually to assess its effectiveness, and must be updated to accommodate new equipment or procedures, or modifications thereof. The Chemical Hygiene Plan must describe the company's compliance program and must be available, upon request, to employees or their designees and to OSHA. The second compliance tool is Employee Information and Training.

A separate Laboratory Standard was developed, partially because laboratory employees generally have a higher degree of education and training than many industrial employees. Because of this, providing information is a major part of the Standard. OSHA requires two (2) things. First, employees should be provided with information to ensure that they are aware of hazards associated with the chemicals in their workplace. Second, this information must be provided when an employee is first assigned to a work area where hazardous chemicals are present, and prior to assignments involving new exposure situations.

The Laboratory Standard requires that employees be provided with five (5) kinds of information. These are as follows:

1. The contents of the Laboratory Standard and its appendices.
2. The location and availability of the Chemical Hygiene Plan.
3. The permissible exposure limits (PELs) for OSHA regulated substances, or the recommended exposure limits for other hazardous chemicals where there is no applicable OSHA standard.
4. Signs and symptoms associated with exposure to hazardous chemicals with which employees may come into contact.
5. The location and availability of reference materials on the hazards, safe handling, storage, and disposal of hazardous chemicals found in the laboratories. This information should include, but is not limited to, Material Safety Data Sheets (MSDSs) received from chemical suppliers.

Although information from suppliers as to the hazards of chemicals can be from sources other than MSDSs, the Standard does require that MSDSs be available to all employees.

Because of the importance of MSDSs and the emphasis put on them by OSHA, a good understanding of MSDSs by employees is of paramount importance to a laboratory's compliance effort.

Suppliers must furnish MSDSs to end users (the laboratory) and the laboratory is obligated to maintain copies of MSDSs received from suppliers of hazardous chemicals. In addition, MSDSs must be readily accessible to employees. All laboratory employees must be trained to know how to read and understand an MSDS. An MSDS consists of nine (9) sections.

Section I: *Material Identification.* Contains name, address, and telephone number of the chemical manufacturer, importer, or distributor. It contains an emergency telephone number (if any) and the chemical identity used on the product label, which should match the product label.

Section II: *Ingredients and Their Hazards.* Includes chemical and common names of all ingredients that have been determined to be health hazards and that comprise 1% or greater of the composition. It lists any carcinogenic ingredient which comprises 1% or greater of the composition, and it gives threshold limit values (TLVs) or permissible exposure limits (PELs) for all hazardous ingredients.

Section III: *Physical Data.* Lists parameters such as vapor pressure, specific gravity, boiling point, melting point, vapor density, general appearance, solubility in water, and odor.

Section IV: *Fire and Explosion Hazard Data.* Provides flashpoint, upper and lower explosion limits, extinguishing media, needed fire fighting equipment, and autoignition temperature and flammability limits.

Section V: *Reactivity Data.* Provides information on how this substance interacts with other substances. Potential to react, and produce fire or explosions or new toxic substances are explained. Conditions to avoid and information on polymerization is also given.

Section VI: *Health Hazard Information.* Gives signs and symptoms of exposure, medical conditions aggravated by exposure, primary route(s) of entry, carcinogenic (mutagen or teratogen) designation, emergency first aid procedures, and threshold limit value (TLV) and/or permissible exposure limit (PEL).

Section VII: *Spill or Leak Procedures.* Lists evacuation requirements, ventilation requirements, clean-up procedures, clean-up materials, waste disposal requirements, and personal protective equipment needed for cleanup.

Section VIII: *Special Protection Information.* Deals with precautions while working with a hazardous substance, and lists ventilation requirements, respiratory equipment needed, other personal protective equipment required, and first aid equipment.

Section IX: *Special Precautions and Comments.* Includes items not addressed previously, such as engineering controls, work practices (not smoking, etc.), and handling instructions.

The end of the MSDS indicates source, date prepared, and sign offs. The MSDS is such an important document in the overall picture of laboratory compliance that its use, and training in its use, cannot be overstated.

Providing information is only the first step. Employees must be trained to understand the information. The Standard requires that employers accomplish two things during training. The first is to provide employees with sufficient training to ensure that they aware of the hazards of the chemicals in their workplace. The second requirement is to provide this training at the time of the employee's initial assignment to a work area where hazardous chemicals are present, and prior to assignments involving new exposure situations. Further, the Standard requires that employee training include, but is not limited to, methods and observations that can be used to detect the presence or release of a hazardous chemical, such as continuous monitoring devices, odor or appearance that indicates such a release, the physical *and* health hazards of chemicals in the workplace, and measures employees can take to protect themselves from these hazards, including specific procedures that have been implemented to protect employees from exposure to hazardous chemicals. These procedures may include such measures as "standard work practices," emergency procedures, or personal protective equipment.

The laboratory manager will have to comply with the Standard in terms of who must be trained, when training has to be performed, and retraining requirements.

In summary, the OSHA Laboratory Standard can be applied successfully to any laboratory by developing and implementing a Written Chemical Hygiene Plan, Use of Education and Training (particularly the details of the Chemical Hygiene Plan and MSDSs) and an information management system that allows for easy entry and access of data used for documentation required by the Standard.

There are several sources of information that will aid in preparing a Written Chemical Hygiene Plan, such as "Prudent Practices for Handling Hazardous Chemicals in Laboratories," available from

The National Academy Press
2101 Constitution Avenue NW
Washington, DC 20418

and the OSHA Laboratory Standard itself, which can be found in 29 CFR Part 1910. In addition, there are a wide variety of "canned" training programs available, in training manual or video cassette format, that provide materials for training needed to comply with the Standard. Some programs even supply fill in the blank, prewritten Chemical Hygiene Plans. An internal safety program in concert with OSHA Laboratory Standard compliance will provide you with a first-class laboratory that makes the statement, "We Care About Our People."

It is beyond the scope of this book to rehash the actual OSHA Laboratory Standard or to write out a detailed Chemical Hygiene Plan. Instead, the purpose is to highlight requirements and to point out actions that must be taken to achieve conformance. Remember, this is a "Performance Standard,"

which means that details which are specific to any laboratory operation and to the chemicals with which it works, are the responsibility of the laboratory manger/supervisor.

One final note: Although the Laboratory Standard supersedes many of the provisions of the OSHA "Hazard Communication Standard", (29 CFR 1910.1200), it does not supersede everything. Check with the company safety or compliance officer to make sure that all OSHA requirements regarding hazardous chemicals are being followed.

REFERENCES

Federal Register, Vol. 55 No. 21 Part 1910, Washington: Office of the Federal Register.

STANDARD OPERATING PROCEDURES

CHAPTER 8: SAFETY

SOP 038: Laboratory Safety Program

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Laboratory Safety Program**	NUMBER: **038**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 5
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To define the components of a comprehensive laboratory safety program.

2.0 SCOPE:

2.1 All analytical laboratories.

3.0 RESPONSIBILITY:

3.1 Laboratory management, Safety administrator, Chemical hygiene officer.

4.0 FREQUENCY:

As per Procedure.

5.0 PROCEDURE:

5.1 Develop a written safety program consisting of the following:

5.1.1 Safety committee membership

Form a safety committee, consisting of laboratory workers and representatives of management.

5.1.2 Safety meetings

Hold safety meetings monthly, and let a different employee speak on safety topics each month. Discuss current safety issues plus status of any uncorrected safety problems.

5.1.3 Safety inspections

Conduct laboratory safety inspections monthly. Issue deficiency report, and require correction by the following month, except for critical items, which should be corrected immediately.

5.1.4 Safety training

Give comprehensive safety training to all new employees before they start any lab work. Ongoing training is accomplished by way of the monthly safety meetings.

5.1.5 Complying with the OSHA Laboratory Standard

The purpose of the Standard is to protect laboratory employees from adverse effects of hazardous chemicals with which they may come into contact in the workplace. The OSHA Laboratory Standard is cited in the United States Code of Federal Regulations, Title 29, Part 1910. This regulation (standard) applies only where the use of hazardous chemicals meets OSHA's definition of "Laboratory Use of Hazardous Chemicals" and "Laboratory Scale" as defined in the Standard, which is

> A chemical for which there is statistically significant evidence, based on at least one study conducted in accordance with established scientific principles, that acute or chronic health effects may occur in exposed employees. The term "Health Hazard" includes chemicals which are carcinogens, toxic or highly toxic agents, reproductive toxins, irritants, corrosives, sensitizers, hepatotoxins, nephrotoxins, neurotoxins, agents which act upon hematopoietic systems and agents which damage the lungs, skin, eyes or mucous membranes.

There are two principal compliance tools that must be used to achieve the intent of the Standard. The first step is to prepare a written chemical hygiene plan. The written chemical hygiene plan must accomplish two things: protect employees from health hazards associated with hazardous chemicals in the workplace (laboratories) and keep exposures below the limits specified in the Standard. To accomplish these two things, the written plan must include many of the elements defined in the Standard such as the following:

5.1.5.1 Standard safety and health related operating procedures that must be followed when laboratory work involves the use of hazardous chemicals.

5.1.5.2 Criteria that will be used to determine and implement control measures needed to reduce employee exposure to hazardous chemicals, such as engineering controls, use of personal protective equipment, and personal hygiene practices.

5.1.5.3 Procedures to ensure that fume hoods and other personal protective equipment are operating properly and specific actions to be taken to ensure that this equipment will function properly and provide adequate performance at all times.

5.1.5.4 Provisions to make sure that employees will be given information and training specified by the Standard in its section on "Employee Information and Training."

5.1.5.6 Definitions of the circumstances under which a particular laboratory operation, procedure, or activity will require prior approval by the employer.

5.1.5.7 Provisions for medical consultations and examinations in accordance with the section of the Standard, "Medical Consultation and Medical Examinations."

5.1.5.8 Designation of personnel responsible for implementing the Chemical Hygiene Plan, including assignment of a "Chemical Hygiene Officer" and establishment of a "Chemical Hygiene Committee."

5.1.5.9 Provisions for additional employee protection when working with particularly hazardous substances, such as select carcinogens, reproductive toxins, or substances having a high degree of acute toxicity.

5.1.6 The OSHA Laboratory Standard requires review of the written chemical hygiene plan at least annually to assess its effectiveness, and the plan must be updated to accommodate new equipment or procedures, or modifications thereof. The Chemical Hygiene Plan must describe the company's lab compliance program and must be available upon request to employees or their designees and to OSHA.

5.1.7 The second compliance tool is Employee Information and Training. First, employees should be provided with information to ensure that they are aware of hazards associated with the chemicals in their workplace, and second, this information must be provided when an employee is first assigned to a work area where hazardous chemicals are present, and prior to assignments involving new exposure situations. The Laboratory Standard requires that employees be provided with five (5) types of information. These are as follows:

5.1.7.1 The contents of the Laboratory Standard and its appendices.

5.1.7.2 The location and availability of the Chemical Hygiene Plan.

5.1.7.3 The Permissible Exposure Limits (PELs) for OSHA regulated substances, or the recommended exposure limits for other hazardous chemicals where there is no applicable OSHA standard.

5.1.7.4 The signs and symptoms associated with exposure to hazardous chemicals with which employees may come into contact.

5.1.7.5 The location and availability of reference materials on the hazards, safe handling, storage, and disposal of hazardous chemicals found in their laboratories. This information should include, but is not limited to, Material Safety Data Sheets (MSDSs) received from chemical suppliers.

5.1.8 Although information from suppliers as to the hazards of chemicals can be from sources other than MSDSs, the Standard does require that MSDSs be available to employees. Because of the importance of MSDSs and the emphasis put on them by OSHA, a good understanding of MSDSs by employees is of paramount importance to a laboratory's compliance effort. Suppliers must furnish MSDSs to end users (the laboratory), and the laboratory is obligated to maintain copies of MSDSs received from suppliers of hazardous chemicals. In addition, MSDSs must be readily accessible to employees. All laboratory employees must be trained to know how to read and understand an MSDS.

5.1.9 Training Under the OSHA Laboratory Standard

The Standard requires that employers accomplish two things during training. The first is to provide employees with sufficient training to ensure that they are aware of the hazards of the chemicals in their workplace. The second requirement is to provide this training at the time of the employee's initial assignment to a work area where hazardous chemicals are present, and prior to assignments involving new exposure situations. Further, the Standard requires that employee training must include, but is not limited to, methods and observations that can be used to detect the presence or release of a hazardous chemical, such as continuous monitoring devices, odor or appearance that indicates such a release, the physical and health hazards of chemicals in the workplace, and measures employees can take to protect themselves from these hazards, including specific procedures that have been implemented to protect employees from exposure to hazardous chemicals. These procedures may include such measures as "standard work practices," emergency procedures, or personal protective equipment.

5.1.10 Management Responsibility Under the Standard

Laboratory managers will have to comply with the Standard in terms of who must be trained, when training has to be performed, and retraining requirements.

5.2 Documentation:

5.2.1 Safety committee membership

Formation of the safety committee, including a roster of its membership, must be documented.

5.2.2 Safety meetings

Minutes of monthly safety meetings should be recorded and preserved as a record of safety training and correction of safety deficiencies.

5.2.3 Safety inspections

The results of all safety inspections should be documented to include findings, safety inspection reports to management, and follow-up documents related to correction of safety deficiencies. This documentation is to be preserved as a record of safety compliance.

5.2.4 Safety training

Document all training sessions with attendance sheets, name of trainer, training topics, and date the training was given. Preserve all training records in a training file.

5.2.5 Document compliance with the OSHA Laboratory Standard by having on file, a chemical hygiene plan and a complete set of MSDSs, plus documentation cited in sections 5.2.1 through 5.2.4

6.0 HISTORY:

6.1 REVISION 0: Supersedes - Original
Reason - N/A

CHAPTER

9

SPACE System of Laboratory Management: Laboratory Performance and Integrity

9.1 PRODUCTIVITY

Maximum productivity can be realized by applying many of the management tools cited in chapter 4, "Tools of the Trade." Some of the tools have a direct impact on day-to-day operations, while others are broader tools that affect not only productivity, but other areas as well. Keep in mind that the focus of this work is "Plain and Simple" management of the analytical laboratory. Therefore, the tools and actions are those actions taken by management/supervision.

The daily tools directly geared towards productivity are

- Self-Contained Paperwork System (3.1)
- Task-Oriented Workload (3.2)
- Support Systems (3.3)
- Work Hour Matching (3.4)
- Total Immersion Supervision (5.1)
- SWA with Intercomm (5.2)
- Accelerated Problem-Solution Loop (5.4)
- Computerized Tracking (5.5)

Broader tools geared towards productivity are

- Passenger Removal (4.1)
- Training (4.2)
- Safety/Housekeeping Awareness (3.5)
- Laboratory Geography and Technology (6.1)
- Quality Assurance (7.1)

The daily impact tools are in fact applied each and every day. *Self-contained paperwork* (worksheets) coupled with *task-oriented workload* (parallel mode) minimizes analysis, documentation, and audit time. *Support systems* maximize the amount of time spent by analysts on analytical work, while *SWA with intercomm* guarantees proper prioritization of work and efficient communications between the laboratory and its customers. *Total-immersion supervision* in concert with an *accelerated problem-solving loop* insures that the laboratory manager/supervisor will have current information on all activities and will be able to channel resources or make adjustments in a timely fashion in response to problems that develop, or to changing priorities or manpower availability. *Work-hour matching* maximizes laboratory resources (equipment not sitting idle on weekends, for example) while *computerized tracking* of workload offers the laboratory manager/supervisor an overall snapshot of his or her current workload at any point in time.

The broader impact tools, while they affect daily operations, are themselves better classified as ongoing, long-term management tools that are subject to adjustment over time.

Passenger removal is accomplished by employee evaluation over some period of time. It is suggested that a probationary period at the beginning of employment be utilized for this purpose. If someone can't perform up to required standards and is clearly a passenger, then in order to maintain maximum productivity, the passenger must be removed from passenger status, either by retraining, transfer to a more suitable job (if available) or termination (as a last resort). The performance of individuals in the laboratory has a direct and immediate impact on daily productivity. With this in mind, passenger recognition and removal(if needed) is a must.

Training is also an ongoing, long-term proposition that impacts on daily performance and must be conducted, not only by company trainers, but also by the laboratory manager/supervisor as part of daily total-immersion supervision.

Safety, like training is a long-term activity that is applied daily but administered over a long period of time and is constantly changing in its requirements. It too can be applied and reinforced daily by management, using total-immersion supervision.

Laboratory geography and technology is a long-term planning issue that is usually dealt with at budget time. However, the laboratory manager/supervisor must always be on the lookout for opportunities to enhance productivity by rearranging laboratory geography or by introducing new technology that will enhance efficiency and/or reduce the cost of laboratory operations.

Finally, *quality assurance,* while a long-term program, will benefit daily productivity in that it assures continuous reliability of equipment operation and analytical results. This makes problem-solving very simple and efficient, and in the case of a "bad result," allows for treatment of the "bad" data in a logical fashion. If equipment problems and issues, such as the integrity of standards and reagents or methodology, can be rapidly ruled out, the more arduous task of resampling and retesting can be initiated without delay (almost concurrently). The quality assurance measures described in chapter 7, coupled with a preventative maintenance program that involves planned, regularly scheduled equipment servicing (HPLC pump seal changes, GC detector cleaning, or pH electrode reconditioning for example), if carried out diligently, will impact dramatically on both daily and long-term productivity. The end result is reduced down-time and the ability to manage

daily events, as opposed to a disruptive laboratory climate where every problem that occurs is a big surprise.

Since the analytical laboratory is a service organization which provides analytical results to its customers, those results are the life blood of the laboratory. With this in mind, there must be a high degree of confidence in each and every piece of analytical data that is generated and released for publication.

Accuracy, like productivity, can be attained by applying the right combination of laboratory management tools. There are four "Tools of the Trade" that will be applied towards production of accurate laboratory results. These are as follows:

1. Passenger Removal (4.1)
2. Training (3.5)
3. Laboratory Geography and Technology (6.1)
4. Quality Assurance (7.1)

Passenger removal is important to accuracy for the obvious reason that if an analyst is a passenger (incompetent or otherwise), his or her work will always be suspect. *Training,* especially in laboratory SOPs and analytical methodology, is also crucial to production of accurate data, simply because a properly trained individual is better prepared to know what to do and how to do it. With regard to *laboratory geography and technology,* the geography won't do anything for accuracy, but the technology might, and probably will. An example is an HPLC method for components of a mixture versus wet chemical methods. The specificity gained by use of a chromatographic procedure will almost certainly improve the accuracy of the analysis. One will have to decide on a case-by-case basis what is best for their own analytical requirements.

While the items just discussed (passenger removal, training, and technology) are important in achieving and maintaining accuracy, the main key to accuracy is a strong laboratory *quality assurance* program. In addition to the quality assurance measures described in chapter 7, a more detailed look at the use of control samples as a means of assuring laboratory efficacy will be taken.

9.2 ROCK SOLID RELIABILITY

While reliable standards, equipment calibration, and strong documentation are all critical to accuracy, control samples are the "icing on the cake." Control samples are laboratory prepared commercial product that contains a known quantity of analyte or analytes, or if the laboratory preparation cannot match the product matrix exactly (many times the case), a large quantity of actual production product is used. The control sample is subjected to analysis by different analysts from more than one laboratory (at least two), if possible, to produce a minimum of 12 different analyses (more is better, at least 20 is recommended). The individual analyses are subjected to statistical evaluation to produce a pooled mean and standard deviation for each analyte. Then, for each analytical run of that product, in addition to running standards with the sample, the control sample is also run. If the analytical results for a control sample for any particular parameter are within plus or minus two

(±2) standard deviations (sigmas) of the pooled mean, then the results of the sample analyses for that parameter will have an extremely high level of confidence in terms of accuracy. In addition, it is a strong indicator that the instruments, balances, and in fact, any steps used in the process of sample analysis are reliable. A control sample is the best single indicator of analytical laboratory performance. For it to come out within acceptable limits, everything else has to be functioning correctly. And, with all those other quality assurance procedures in place as well, serendipity is almost certainly ruled out as a factor.

Control samples should be labeled and documented as to preparation, analysis, and statistical treatment. Several control samples should be available for each major analysis, and they should be replaced before expiration of shelf life. Shelf life can be determined from known chemistries or by comparing the analysis of an existing control to that of a freshly made control. Discard the old control when its analysis versus the fresh control has changed by some amount defined by Quality Assurance or R&D. The time it takes for deterioration of a control, as determined empirically by analysis versus a fresh control, can be used as a reliable and reasonable shelf life.

If a control sample analysis is out of spec, it could indicate analyst error, instrument problems, or that the control itself has changed. An answer has to be found before continuing with the analysis of samples.

For illustrative purposes, the evolution of a single analyte control sample, prepared as follows will be examined:

1. A control sample is prepared by an Analytical R&D group for HPLC analysis of Component [A] in a commercial product. A sufficient quantity (one pound or one quart, for example) is prepared.
2. The sample is well mixed and split into two separate portions.
3. One portion is retained by Analytical R&D, and the other is submitted to the Quality Control laboratory.
4. Two chemists in Analytical R&D and two chemists in Quality Control each perform six (6) separate assays for a total of twenty-four (24) analyses.

Results (meq/gm) are shown in tabular form (Tables 9.1–9.2). In addition, line plots are shown (Figures 9.1–9.3) containing individually plotted data points and lines representing the mean plus the upper control and lower control limits (±3 sigmas from the mean).

The data show the control to be suitable for use. Relative standard deviations are low, and the means are similar from chemist to chemist and for the pooled mean. In addition, the process capability is greater than 1.3, indicating that the analysis is in control. Process control examples, plus a more detailed discussion of statistical parameters, is given in chapter 12. Step-by-step instructions for preparation and use of control samples are presented at the end of this chapter in SOP 039, "Preparation and Use of Control Samples."

Before proceeding further, it must be pointed out that the use of control samples is designed to provide assurance that a particular analysis is in control. That is its only job. It tests the entire

Table 9.1. Illustrative Single-Component Control Sample Statistical Data

	ANALYTICAL RESULTS—MILLIEQUIVALENTS PER GRAM			
Analysis #	**[QC Chemists 1 & 2]**		**[R&D Chemists 1 & 2]**	
1	21.23	21.48	21.52	21.69
2	21.05	21.11	21.15	21.89
3	21.77	20.99	21.31	21.62
4	21.00	21.74	21.93	22.10
5	21.87	21.85	21.02	21.37
6	21.45	21.58	21.62	21.26
Mean	21.40	21.46	21.43	21.66
Sigma	0.37	0.34	0.33	0.31
%RSD	1.71	1.58	1.54	1.45

Table 9.2. Pooled Results—24 Analyses

Mean Value—Milliequivalents per Gram	21.48
Sigma (Standard Deviation)	0.33
%RSD (Percent Relative Standard Deviation)	1.55
Upper Control Limit (Mean plus 3 Sigmas)	22.47
Lower Control Limit (Mean minus 3 Sigmas)	20.49
Cp Value (Process Capability)	2.18

PRODUCT SPECIFICATIONS = 19.44 - 23.76 MEQ/GM

analytical process, the whole system, including the analysts. Accuracy, on the other hand, is best controlled by use of appropriate analytical standards and is assured, along with specificity, linearity, specificity, and ruggedness, through the process of analytical methods validation. When a control sample is accurately prepared from laboratory standards, an additional gauge of accuracy is gained; however, its primary goal is still as an indicator of analytical method control.

Figure 9.1. Control sample analyses quality control samples.

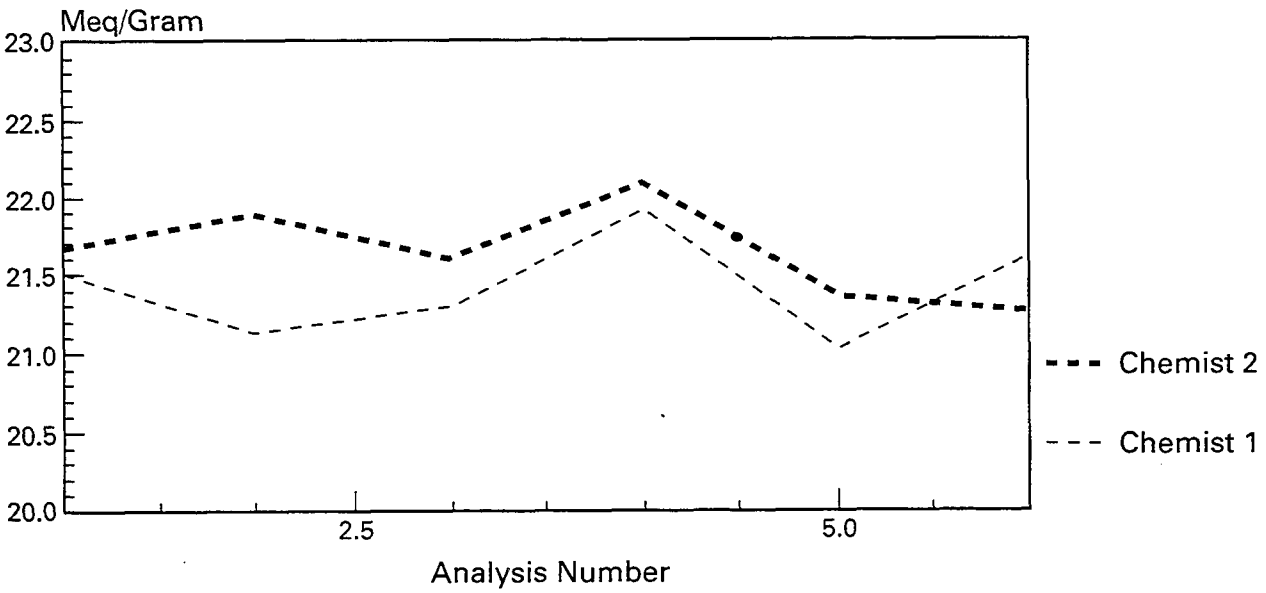


Figure 9.2. Control sample analyses R&D chemists.

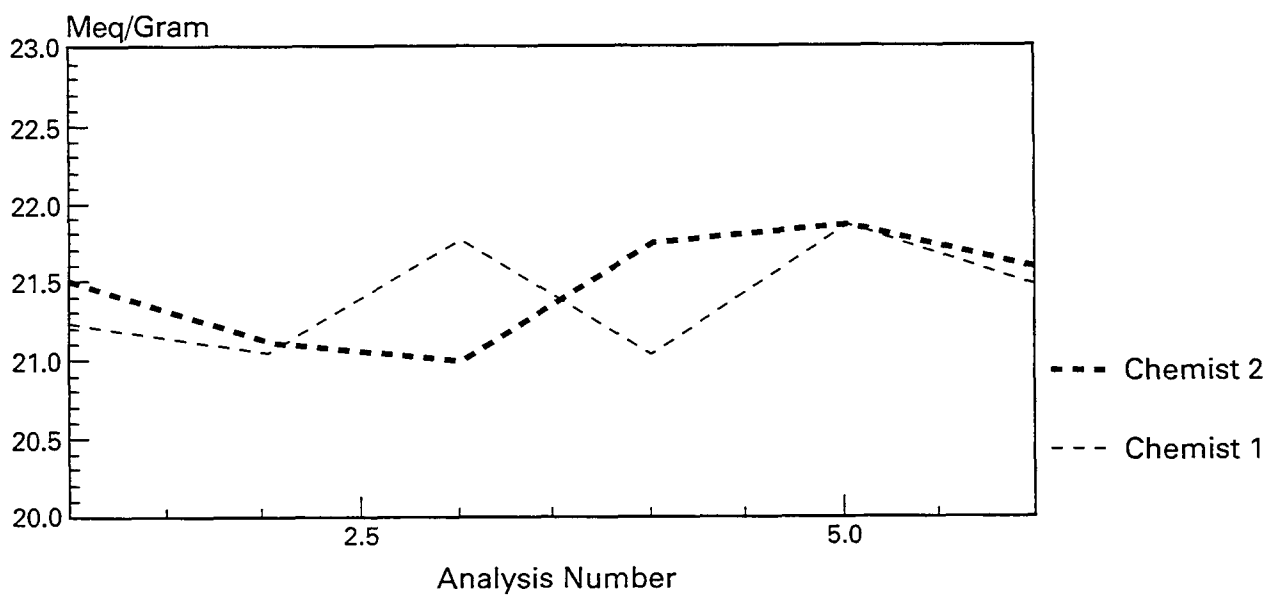
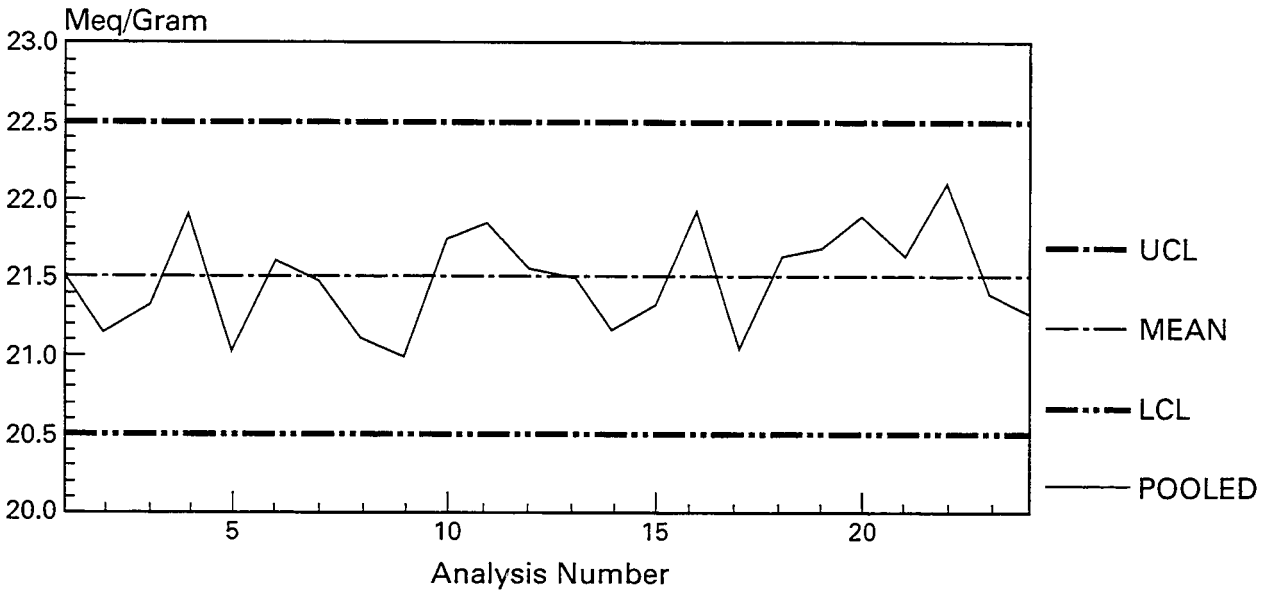


Figure 9.3. Control sample analyses pooled data for 24 points.



For HPLC analysis, assume that the acceptance criteria for a new control is an RSD (Relative Standard Deviation) of 2 percent or less for each analytical parameter. Since the individual groups of data plus the pooled mean meet this criterion, the control sample results are deemed acceptable. For daily use of control samples, analytical results for the control should be within plus or minus two (±2) standard deviations (sigmas) from the established mean. Plus or minus two sigmas is the 95 percent confidence level and should be set as the acceptance criterion for controls when running them with actual samples.

Please note that there are many far more sophisticated tools for data analysis, but the goal here is to use a "Plain and Simple" tool as opposed to cluttering up the laboratory with integrals and differential equations. This is a simple and widely accepted technique that works.

Keep in mind also that accuracy has to be achieved while maintaining productivity. Control samples take time to prepare and to run. Therefore, it might not be practical to have a control for every possible sample that the laboratory will encounter. From a practical standpoint, the 80/20 rule is often applied, which means that control samples are first prepared for the 20 percent of the products that represent 80 percent of sales. As productivity increases and as time permits, others can be added.

A control sample, if available, should be run with every set of analyses. A value obtained by analysis for the control that is within plus or minus two (±2) standard deviations (sigmas) from the mean is a good indicator that the analysis is functioning correctly.

By combining the use of control samples with the quality assurance measures discussed in the previous chapter, a high level of confidence in analytical data is virtually guaranteed.

9.3 CREDIBILITY

The issues of safety, productivity, and accuracy have just been addressed, using the Tools of the Trade to achieve each. Having an analytical laboratory that is safe, productive, and turns out accurate results is certainly the goal of any laboratory manager/supervisor. But is this enough? Perhaps not.

One of the most important aspects of laboratory management is that of credibility. A manager may have confidence in his or her laboratory, but do others? It is extremely important for the analytical laboratory, as a service organization, to have the respect and trust of its customers.

Credibility is attained through a combination of actions. An analytical laboratory that is productive (on-time work), accurate (results are reliable), and has a low or zero accident rate (safe) will surely have a high degree of credibility. It will be well thought of as a reliable and trusted service organization. Using the right management tools, particularly a strong quality assurance program coupled with a vigorous ongoing training program, will result in an analytical laboratory whose results are reliable and rarely questioned by those outside the laboratory organization.

But what about inside the laboratory organization? The laboratory manager/supervisor must constantly challenge the system. In addition to the techniques already presented, there is one more thing that needs to be done from within to ensure laboratory credibility—test the analysts.

Quality assurance measures such as calibration and maintenance will monitor the performance of balances and other instruments, and standards and control samples will serve to monitor analytical results. But what about the analysts themselves? The final step to achieving documentable credibility is to test the analysts on a regular, ongoing basis.

Some may ask, why do we need to test the analysts? This author has witnessed laboratories that are totally out of control and have virtually zero internal credibility. On one consulting assignment, the task was to find out why productivity was low and why half of the analyses always had to be repeated.

One look inside this laboratory (a QC lab) told the tale. It was obvious that basic skills, such as proper weighing and pipetting techniques, were not up to par. Each analyst was given a basic analytical exercise to perform, which consisted of "weighing a solid sample, quantitative transfer to a volumetric flask, dissolving the sample in water, diluting to the mark with water, and transferring a volumetric aliquot of the resulting solution into a beaker." Of the analysts who took this "test," a significant number were not able to perform all the required steps without major technique deficiencies. The lesson here is, don't underestimate how bad things can get. The "Storytelling Syndrome" and the "Teacher's Pet Syndrome" can take a heavy toll on any analytical laboratory.

This test, given to experienced, practicing analysts, may seem ludicrous, and was perhaps even a bit insulting, but it served to demonstrate that extreme out-of-control situations can and do exist within the analytical laboratory. Granted, in this particular case, there was only one week allowed for problem identification, and people tend to get nervous under test conditions and might make mistakes that ordinarily would not occur. However, every piece of real data produced by an analyst is important, and by the very nature of their work, analysts are tested each and every time they

perform an analysis. No manager or supervisor wants to hurt people's feelings or to degrade anyone, but managers must have documented evidence of analyst competence (quality) to insure credibility and to provide feedback to the analyst as a continuous improvement tool designed to promote professional growth.

The best way to continuously monitor the quality of the analysts in a professional and unbiased manner is through the use of blind control samples. Regular control samples have their analytical values known to the analyst, and they are run with samples as a *control on the analysis.* Blind controls are control samples that are unknown. They are accurately prepared and subjected to statistical analysis in exactly the same manner as regular control samples. The laboratory manager knows the mean value and upper and lower control limits, but keeps these data confidential. Blind controls can be given dummy lot numbers and submitted as routine samples. Assignment of work must be structured so that each analyst is exposed to each of the blind controls on a regular basis. The results of blind control analyses provides *unbiased control on the skill of the analysts.* All the manager or supervisor needs to do is to compare results generated by an analysts on a blind control with the true values as determined by statistical evaluation of that control. As an additional test of the system, a small percentage (10 percent for example) of the blind controls are purposely selected to be out of specification. The controls that are deliberately prepared to be out of specification provide an additional test of how well SOPs, analysts, and corrective action procedures are working.

Blind control data should be documented, as should any actions taken for the purpose of monitoring systems and correcting problems that may have been detected through the use of blind controls. The combination of standards, controls, and blind controls will assure the highest level of credibility, because data are available to assure that credibility.

STANDARD OPERATING PROCEDURES

CHAPTER 9: LABORATORY PERFORMANCE AND INTEGRITY

SOP 039: Preparation and Use of Laboratory Control Samples

NEWLABS, INC.		LABORATORY PROCEDURE
TITLE: **Preparation and Use of Laboratory Control Samples**	NUMBER: **039**	REV: **0**
WRITTEN BY:	DATE:	PAGE 1 OF 5
REVIEWED BY:	DATE:	
APPROVED BY:	DATE:	EFF. DATE:
APPROVED BY:	DATE:	

1.0 PURPOSE:

1.1 To describe a procedure for preparation and use of laboratory control samples.

2.0 SCOPE:

2.1 All analytical laboratories.

3.0 RESPONSIBILITY:

3.1 Laboratory management, Quality Assurance, Analytical R&D, Laboratory analysts.

4.0 FREQUENCY:

As per Procedure.

5.0 PROCEDURE:

5.1 Standard Control Sample Preparation

5.1.1 A control sample for any product should be prepared by an Analytical R&D group as follows:

5.1.1.1 Prepare a laboratory quantity of about one (1) quart or one (1) Kg of a product by accurately weighing and combining all the ingredients present in that product, using the same formula as that for the actual product.

5.1.1.2 Prepare the laboratory scale product such that each active ingredient is at a concentration that is at the middle or mean value of its specification. For example, if active "X" has a specification of 90–110 mg/g , it should have a concentration in the control sample of about 100 mg/g.

5.1.1.3 Split the control sample into two equal portions.

5.1.1.4 Submit one portion to the analytical lab that does product release testing and retain the other half in analytical R&D.

5.1.1.5 The analytical R&D group should have two (2) separate chemists run six (6) assays each by the analytical method currently in use for the product for which the control sample has been prepared.

5.1.1.6 Similarly, the analytical group that does product release testing should have two (2) separate chemists run six (6) assays each by the analytical method currently in use for the product for which the control sample has been prepared.

5.1.1.7 For each of the four (4) groups of six (6) assays, compute the assay mean, standard deviation, percent relative standard deviation (%RSD), upper and lower control limits, process performance, and process average, adjusted for process performance as follows:

Mean — Sum of assay values divided by number of assays.

Sigma — Standard deviation—calculate using statistics functions on a scientific calculator.

Computed LCL and UCL:

LCL — Lower Control Limit = Mean minus 3 standard deviations.

UCL — Upper Control Limit = Mean plus 3 standard deviations.

These are what the specifications should be, based on actual process data. Of the batches produced, 99.44 percent will fall into this range if statistical variation is normal.

Pp — Process Performance Index.

Pp $\quad \dfrac{(UCL-LCL)}{6s} \quad$ (s = Sigma)

Pp > 1.3 = process in good control.
Pp between 1.0 and 1.3 = process in control but should be watched.
Pp < 1.0 = process out of control.

Ppk — Process average adjusted for process performance.

Ppk $\quad \dfrac{\text{MIN}\,[\,USL - PA\,,\,PA - LSL\,]}{3s \qquad 3s}$

Ppk values should be equal to or slightly less than that of process performance index. They indicate the degree of centering around the mean.

5.1.1.8 Repeat 5.1.1.7 using all twenty-four (24) assays in order to create pooled statistical data for all four (4) chemists.

5.1.1.9 Plot the pooled data on a linear graph, with assay value as the Y axis and assay run number as the X axis. Show mean, UCL, and LCL as straight lines parallel to the X axis.

5.1.2 If the mean values of the individual chemists and that of the pooled mean have an RSD of 2.0 percent or less, and all mean values are less than 2.0 percent relative from the actual value as prepared, the Pp value is greater than 1.3, and the Ppk value is equal to or only slightly less than Pk, then the control may be accepted, as it indicates that the analytical method is in control and that the population of assays run is statistically significant in predicting the behavior of the control under actual conditions of its analytical method. Failing to meet the above criteria, the control sample should be discarded and reprepared.

5.2 Preparation of Blind Control Samples

5.2.1 Proceed as directed in Section 5.1, "Normal Control Sample Preparation," except vary the concentration of actives throughout the specification range. About 10 percent of blind controls should be prepared such that the concentration of active ingredients is slightly above the upper specification limits and/or slightly below the lower specification limit.

5.3 Use of Control Samples

5.3.1 Normal control samples should be run with each analysis to insure that the entire analytical system is performing properly for the method being run. If the assay value for the control is within plus or minus two (2) sigmas of the statistical mean established in Section 5.1, then all other things being equal, any sample analysis conducted during the run can be deemed reliable.

5.3.2 Blind control samples should be submitted to analysts as actual samples from time to time, as a test of analyst performance. Results are submitted as if they were actual samples and compared to the actual blind control sample values, as determined in Section 5.2. The actual values of blind control samples should only be known to management in order for unbiased controls on analyst performance to be maintained.

5.3.3 If a normal or blind control fails to meet its statistical criteria, and no problem is detected with the analytical method (instrument, standards, reagents, weighings, etc.) or with the analyst by way of an informal laboratory investigation, then the control should be discarded and a new control freshly prepared.

5.4 Product Matrices

For most products, the formula is known; thus, the matrix can be duplicated during laboratory preparation of the control sample. However, where the matrix cannot be duplicated, such as with a natural product, the control sample will have to consist of a typical production batch of product. In this case, blind control preparations are not possible.

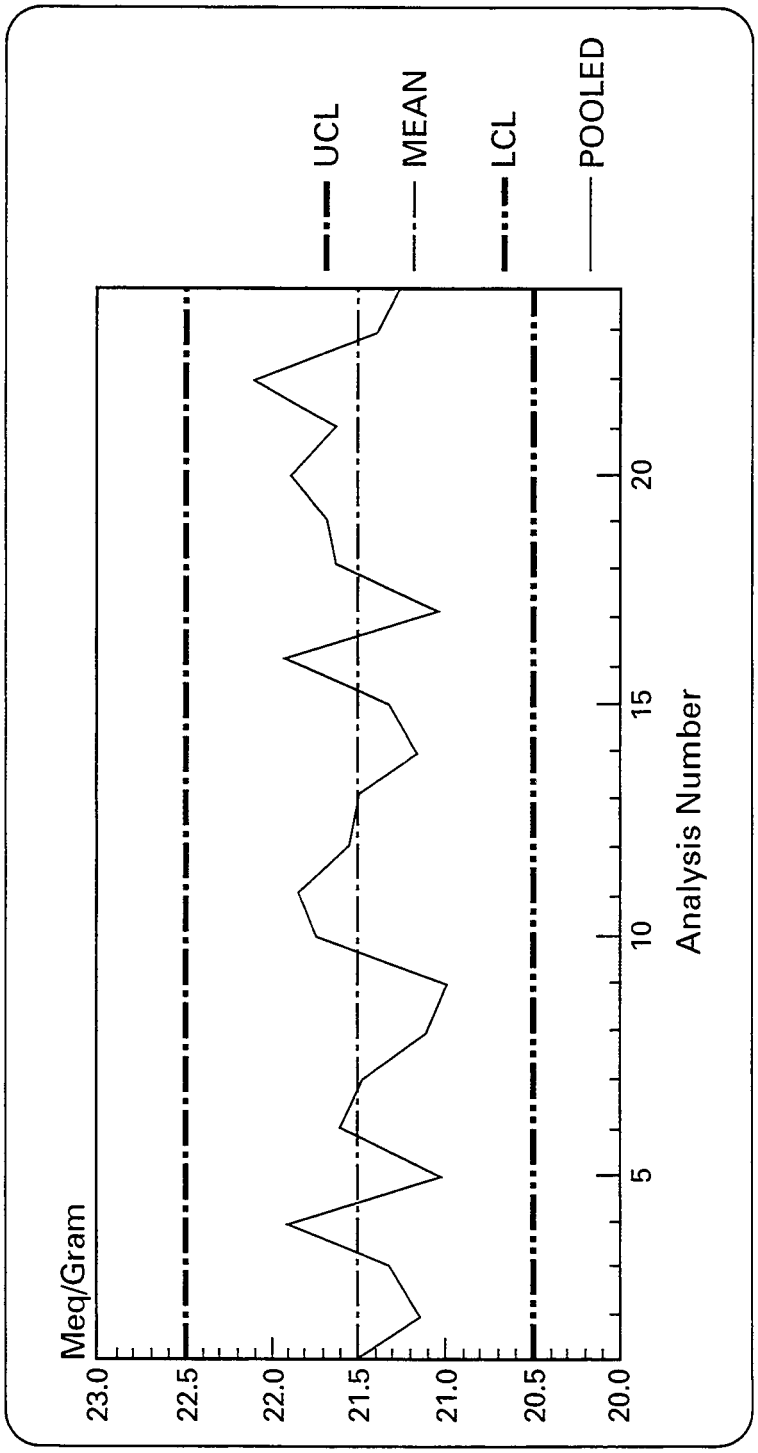
6.0 ATTACHMENT:

6.1 Sample Control Plot—Twenty-Four (24) Assays

7.0 HISTORY:

7.1 REVISION 0: Supersedes - Original
Reason - N/A

Sample Control Plot—Twenty-four (24) Assays



CHAPTER

10

SPACE System of Laboratory Management: Education

10.1 EDUCATION

Education is the final component of the SPACE system. Education is accomplished in two ways: training and professional development.

10.1.1 Training

Training should be provided at commencement of employment in the laboratory (new employee or transfer from another area) and on a continuous basis during the course of each analyst's employment.

A proposed minimum training schedule at commencement of employment is as follows:

1. General Laboratory Practices
    a. Sampling
    b. Receipt of samples
    c. Paperwork procedures
    d. Housekeeping practices
    e. Work schedules
    f. Communications
2. Safety Practices
    a. Internal safety program
    b. OSHA laboratory standard
    c. Evacuation procedures
    d. First aid and CPR
    e. Personal protective equipment

f. Safe handling and disposal of chemicals

g. MSDSs and labeling

3. Quality Assurance Practices

   a. Calibration and maintenance

   b. Documentation

   c. Standards and control samples

   d. Retention samples

   e. Reporting and treatment of data

   f. Statistical quality control

4. Standard Operating Procedures

   a. Review general SOPs with analysts

   b. Review laboratory-specific SOPs with analysts

The above examples are not intended to be a complete list, but rather a starting point from which to launch a sensible training orientation for new analysts. Each company's program will vary with the specific policies of the company. New laboratory employees should be trained in all general procedures needed for their jobs prior to starting actual work. Written SOPs should be the basis for all training related to laboratory procedures.

10.1.1.1 Training Schedule on the Job

On the job training, just like new employee training, is best provided using written SOPs. On the job training can be provided as follows:

- Train by reviewing the appropriate SOP with an analyst prior to that analyst using an instrument or piece of apparatus for the first time.
- Train by reviewing an analytical method or procedure with an analyst prior to the analyst performing the subject method or procedure for the first time.

All training should be repeated at regular intervals for all laboratory employees to insure that each analyst's knowledge and skills remain fresh and up to date. Rotation of work should be arranged so that analysts are exposed to all major procedures on a regular basis. Work rotation will serve to reinforce training continuously.

Another valuable technique is the use of practice samples by analysts when performing a procedure for the first time. This way, the analyst can test his or her grasp of the procedure without worrying about making a mistake. Remember, "bad" data must always be explained and documented. If a nonpractice sample is used for training and the analyst makes a mistake, a documented explanation must follow, and under certain circumstances (another mistake is made on retest and the original analysis cannot be voided), might even result in a batch rejection. However, a practice sample can be chalked up to training without compromising laboratory credibility or exposing the laboratory to regulatory problems.

Blind controls make excellent practice samples since they monitor analyst skill and can be documented for internal use only, as a management tool, without primary exposure to regulatory inspection. However, a well-documented training program, using practice samples, can be useful during FDA inspections as a means of demonstrating a solid and well organized commitment to training.

When running actual samples, out-of-specification data must be explained in a laboratory investigation, using specific retest protocols to overcome any failing results. Practice sample training minimizes failure investigations by allowing the analyst to generate failing results (bad data) during a learning phase of employment, rather than during analysis of actual products or raw materials, where the analytical results affect consumer safety and company profits. Additionally, bad data generated during practice runs, followed by acceptable data for practice samples as training progresses, will show the Agency (FDA) that analysts who are doing actual samples have the appropriate training necessary to do their jobs.

10.1.2 Professional Development

Professional development of laboratory personnel is extremely important for their career growth. This can be accomplished by encouraging (and paying for) memberships in professional organizations, sending employees to professional meetings or conferences, encouraging the reading of professional journals, and promoting and encouraging interaction and exchange of ideas (brainstorming) between laboratory personnel and between laboratory personnel and employees of other departments such as Quality Assurance and Manufacturing. Last, but not least, a vigorous program of continuing education must be encouraged by such means as tuition reimbursement for job-related courses and seminars.

In any organization, people are the most important asset. It is employee performance that will make or break a laboratory (or company), especially in terms of its credibility and overall reputation. Education of employees through a balanced mix of training and professional development, all other things being equal, will provide maximum assurance that laboratory personnel are performing well, now and in the future.

10.2 EDUCATION DOCUMENTATION

Finally, proper management of any training program requires solid documentation. There are many ways to handle this task. Some companies use individual training records within departments, while others have a centralized company training program. The best way to handle training program management is to maintain individual training logs for each analyst, coupled with centralized tracking by use of computers. There are several training tracking management programs on the market. Selection is a matter of which one best fits a company's particular needs.

A typical training software package will normally contain features shown in the following example. In addition to allowing entry of actual training sessions, a listing of employee names and ID, and training program (course) names, a typical training package might also generate a number of reports that give hard-copy printouts of company-wide training activity and training activity by department, by employee, and by course. Exception (tickler) reports might also be available to flag retraining intervals for courses. This type of software makes training management easy and accurate and provides a neat and easy way to show an organized training record to the FDA if needed as

part of a GMP inspection. Typical function menus for training tracking software are shown in Figures 10.1 and 10.2.

In terms of reports, it would be quite useful for the monthly training report to show the percent time spent on training both for each department and company wide for the month and year to date, and to print out individual attendance sheets for each training session. As shown in Figure 10.2, training tracking software should also provide training history by employee or employees, by course or courses, and by department. It should also flag which employees have not taken required courses for their department and display repeat dates for employees needing retraining in a particular area. It would also be convenient if alphabetical lists of employees and training courses could be generated. A well managed and documented training program will not only help with FDA inspections, but will also help with inspections by other agencies such as OSHA, and for pharmaceutical firms using controlled substances, by the DEA (Drug Enforcement Agency).

Figure 10.1. Example of training software main menu.

CODE	SELECTION
<1>	Enter Training Session Data
<2>	Edit Training Data
<3>	Show Report Menu
<4>	Exit Software

Enter Code to Make Selection

Figure 10.2. Example of training reports menu.

CODE	REPORT TYPE
<1>	Monthly Training Report
<2>	Show Training File Contents
<3>	Print List of Training Courses
<4>	Print List of Name & I.D. Numbers
<5>	Track Training by Employee
<6>	Track Training by Course
<7>	Track Training by Department
<8>	List Required Courses—Each Department
<9>	Exception (Tickler) Reports

Enter Code to Select Report Type

10.2.1 A Final Reminder on Documentation

As described in chapter 4, section 4.2.3, formal training sessions held at regular intervals are not the only training sessions that need to be documented. Conversations between supervisors and analysts, where the supervisor answers questions or explains something, is also training, and should be documented. Take advantage of the training that is done during the course of work as part of *total-immersion supervision.* This will help achieve the organization's or department's target for percentage of work hours spent on training.

While the SPACE system provides the sequence of steps, using the Tools of the Trade plus new and expanded concepts needed to lay out a comprehensive management plan, the responsibility for the design and implementation of an effective laboratory management plan clearly lies with the laboratory manager/supervisor. The tools, techniques, and guidance provided herein are just that, tools, techniques, and guidance. Laboratory managers and supervisors have the task of designing and implementing their own successful laboratory management program.

CHAPTER

11

Saying It With Flowcharts

This chapter is designed to help the reader put the information presented thus far into focus. It was decided to put the laboratory management techniques described herein into flowchart form to better aid in developing a comprehensive management system for the laboratory and to assist in daily supervision of the laboratory.

Flowcharts such as those shown in Figures 11.1 through 11.4 provide a quick reference tool for monitoring day to day activities within the laboratory. They show a step-by-step sequence of events for various phases of analytical laboratory operations. When used individually and in combination, they provide an overall plan outline for plain and simple management of the analytical laboratory. Reference to chapters and sections are included where applicable.

The sample flowcharts should provide a convenient quick reference for the laboratory manager for all main operational functions of the pharmaceutical analytical laboratory. The small numbers in parentheses are references to tools of the trade that apply to the activity next to which they are positioned. For example, on Figure 11.1, the reference (3.2) in the box labeled "Work done in parallel with other samples," refers the reader to chapter 3, section 3.2, "Task-Oriented Workload," which provides guidance for how to execute the particular action step shown in the flowchart box.

The flowcharts presented here are meant to provide general guidance. Readers are urged to design flowcharts that meet the management needs of their own laboratories.

Figure 11.1. Flowchart for laboratory samples.

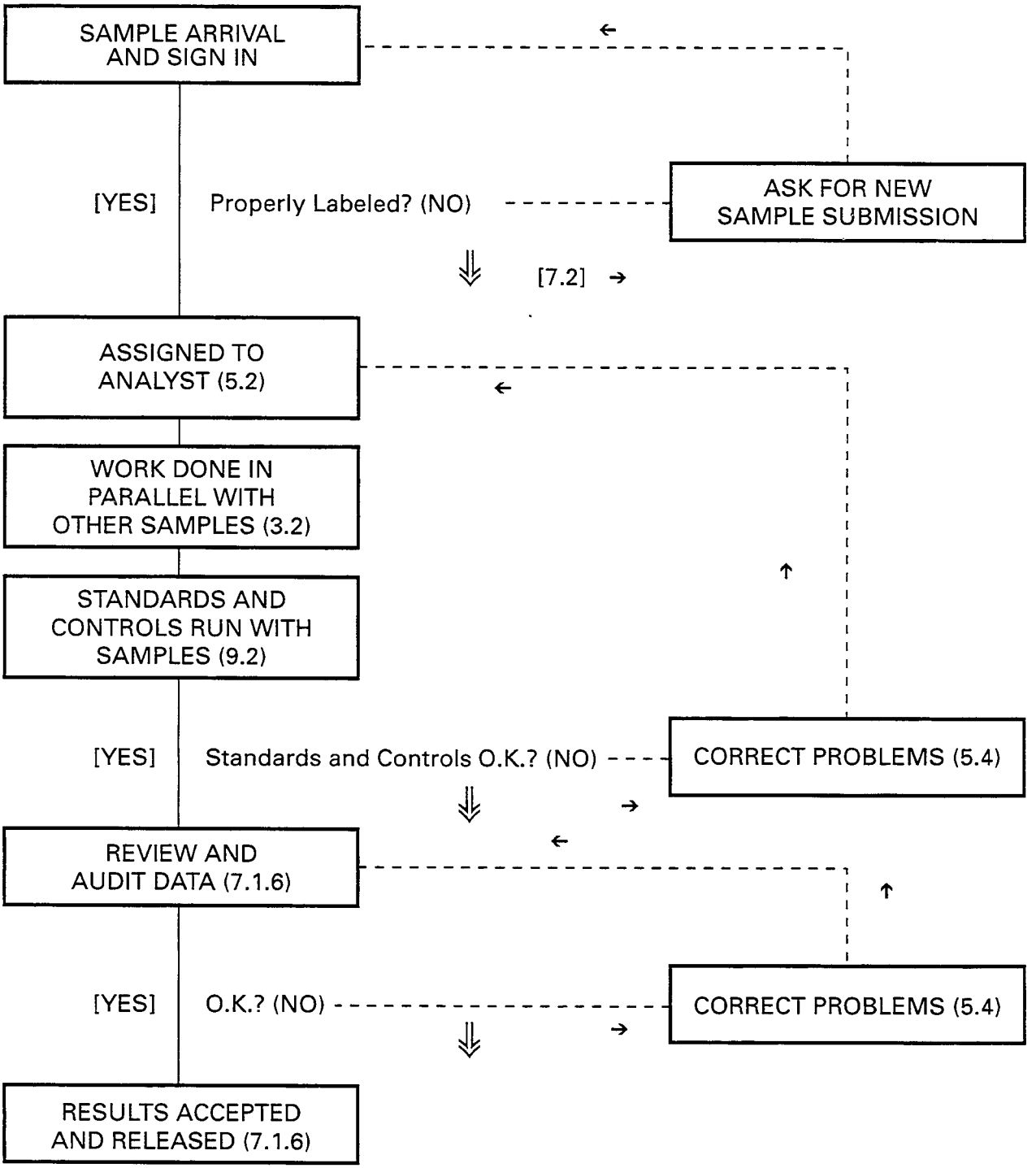


Figure 11.2. Supervisory flowchart.

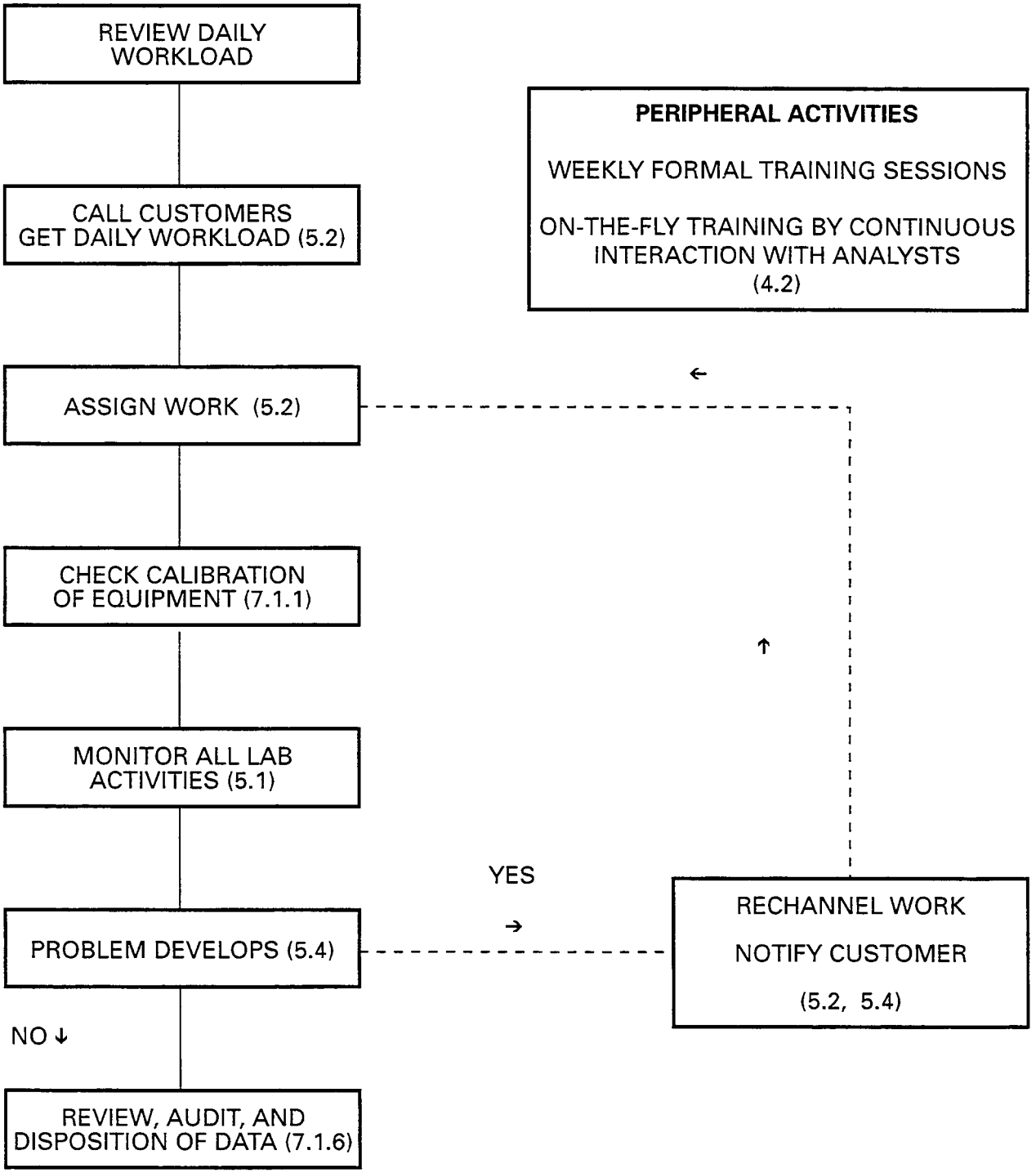


Figure 11.3. Quality assurance flowchart.

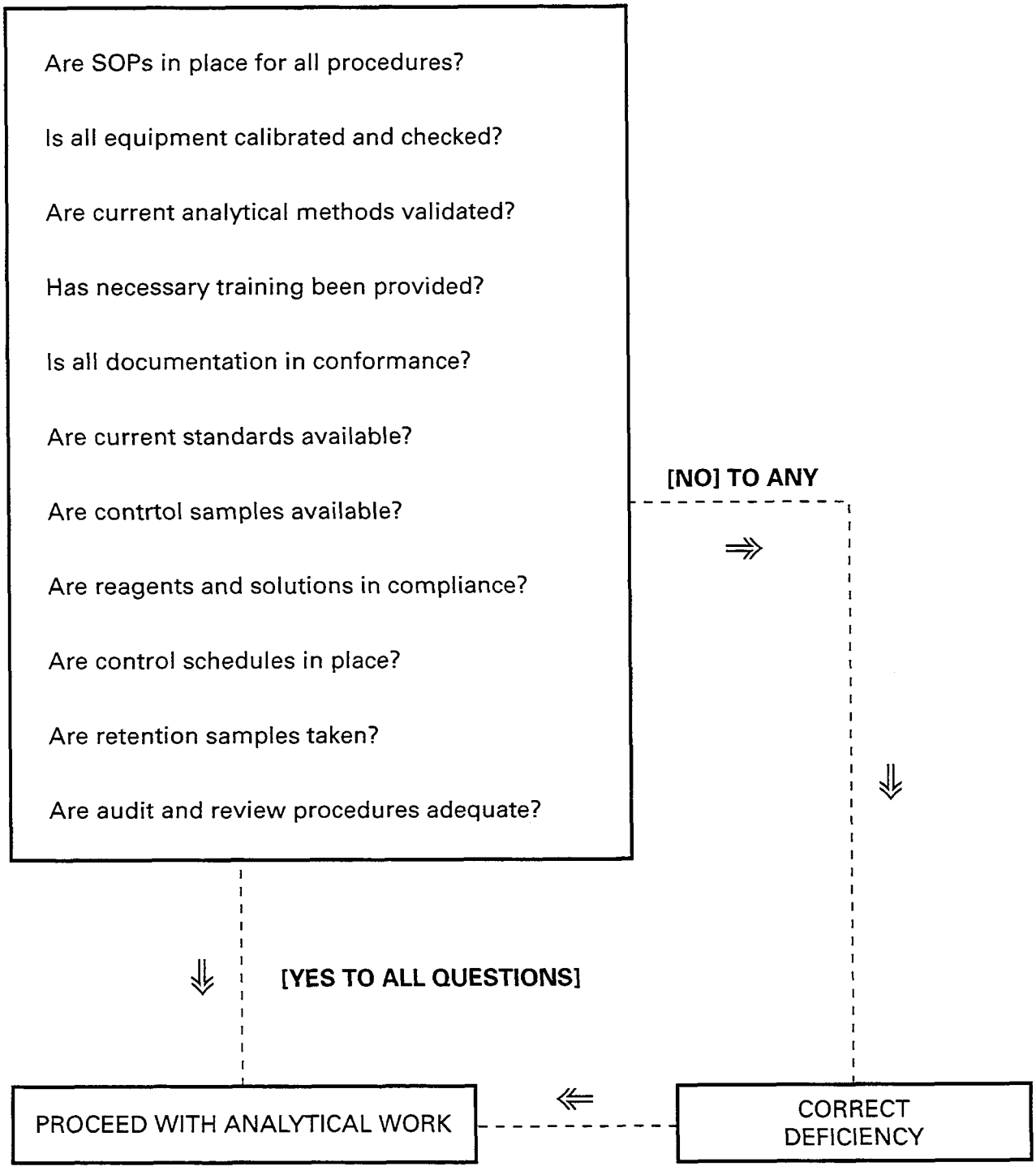
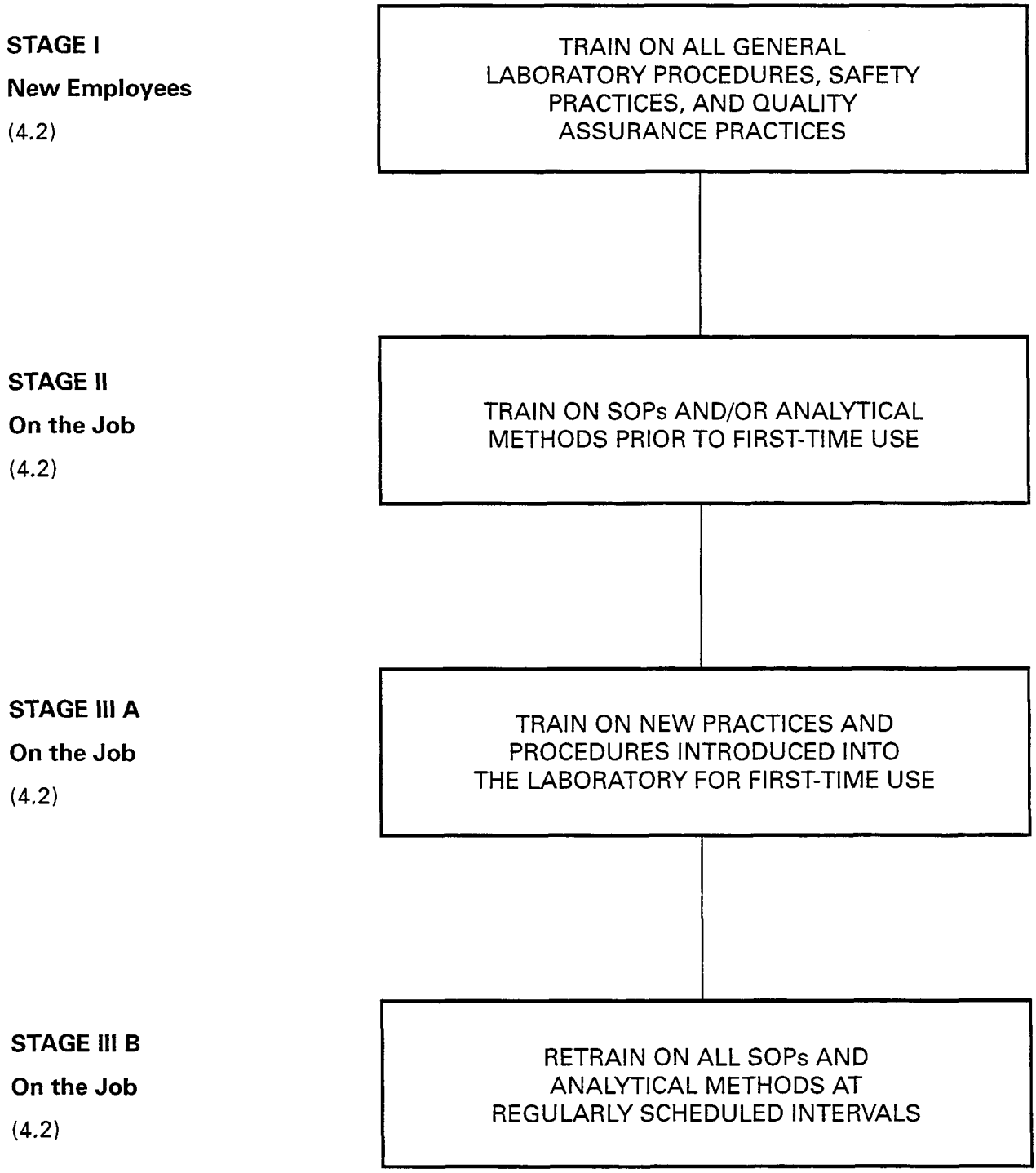


Figure 11.4. Training flowchart.



CHAPTER

12

People, Places, and Things

Previous chapters examined the problems faced by today's analytical laboratory, went on to explain in detail the 14 "Tools of the Trade," and then presented components of the SPACE system of laboratory management as a means for developing an overall management scheme for the analytical laboratory. This chapter will touch upon several issues that need more detailed discussion and which will complement the information presented thus far in design and development of a comprehensive laboratory management plan. Earlier chapters dealt with management of the analytical laboratory in a way that attempted to illustrate means and ways applicable to most analytical laboratories. This chapter, by contrast, deals with issues that are more laboratory specific, and in addition, looks at some personnel matters and presents a diversified assortment of problem-solving case histories.

The "People" section covers management of relationships between professionals in the laboratory, focusing on such issues as job satisfaction, motivation, discipline, and advancement. "Places" focuses on the problems and special requirements of specific types of analytical operations, such as Quality Control and R&D. "Things" presents a variety of case histories where application of laboratory management techniques described herein have had a significant positive impact on actual analytical laboratories, demonstrating quite clearly that a wide variety of situations can be managed in a manner that is not only plain and simple, but also easy to understand.

12.1 PEOPLE

It is gratifying for laboratory managers to know that safety, productivity, accuracy, credibility, and education are up to par, but there is more to it than just that. Yes, instruments, validations, documentation systems, and other physical components of the laboratory are managed, but first and foremost, people are managed.

In order for any organization to be totally successful, it must promote the welfare of its employees through training, recognition, ergonomics, and communications. Most people, during their working years, spend about one-third of their time at work. Therefore, job satisfaction is of paramount

importance in maintaining a stable and committed workforce. Factors such as productivity, teamwork, loyalty, attentiveness to detail, good communications, professional growth, and profitability are all directly influenced by the *quality of life* in the workplace.

12.1.1 Job satisfaction

It is extremely important for the laboratory manager to know how to measure his or her peoples's attitudes about their overall jobs, especially in areas such as quality of supervision, working conditions, nature of work, training, compensation, interaction with coworkers, and whether or not they feel a sense of appreciation for their efforts. The following steps outline an effective method for measuring the degree of job satisfaction among a group of employees:

A. Determine satisfiers and dissatisfiers.

B. Compile results of survey and categorize into subject areas.

C. Present results of survey to the whole group.

D. Form action teams within each group.

E. Facilitate action team meetings.

F. Facilitate group meetings.

G. Re-do survey every six months.

H. Ongoing action teams.

The above steps outline actions that will not only identify what employees are feeling and thinking, but also will result in a favorable quality of life in the laboratory that will meet management objectives consistent with the SPACE system and tend to create and maintain a work environment that is both fun and rewarding.

Step [A], determining satisfiers and dissatisfiers, finds out what employees like and dislike about their jobs. When asked to discuss the positives and negatives of their jobs, some employees will speak up, and others will not. The satisfier/dissatisfier technique, from experience, is usually effective in evoking honest responses from people about job satisfaction and/or dissatisfaction. A form such as that depicted in Figure 12.1 is distributed to each employee. They are filled out, collected by an employee representative or representatives and turned into the laboratory manager.

The rules for filling out the satisfier/dissatisfier form are as follows:

- No names are used (total anonymity).
- Be specific (say that a particular instrument doesn't work rather than, "nothing in this place ever works right").
- Be honest and constructive.
- Don't mention names (Say "my supervisor is unfair" rather than, "Bob Smith, my supervisor, is unfair").
- Forms must be filled out independently and in private so as not to influence others.

Figure 12.1. Job satisfiers—dissatisfiers.

Satisfiers	Dissatisfiers

Figures 12.2 and 12.3 list actual job satisfiers and dissatisfiers collected from the laboratory employees of an actual pharmaceutical manufacturing firm. Many of their feelings were not previously known by management, because the workers were never asked how they felt or what they thought and most would just keep quiet as they updated their resumes. When asked about their jobs, using anonymous satisfier/dissatisfier forms, the response was unanimous. No one felt threatened, and because of the anonymity, management was both enlightened and pleasantly surprised, as the information collected from this exercise and the actions taken subsequent to the survey resulted in many benefits for that company, including better morale and lower turnover.

The satisfiers and dissatisfiers listed in Figures 12.2 and 12.3 are the individual perceptions of a large and diverse group of individuals. Many of these satisfiers and disatisfiers are redundant, demonstrating the similarity between perceptions by individuals within any given workforce.

Step [B] calls for compilation of the survey results and formation of categories to classify the satisfiers and dissatisfiers into a logical pattern upon which positive action can be initiated. When this was done for the satisfiers, the largest percentage was relations between coworkers followed by working atmosphere. For dissatisfiers, poor supervision led the pack, followed fairly evenly by training, disorganization, recognition, and interrelationships with peers.

Step [C] presents results of the satisfier/dissatisfier survey to all the employees at a group meeting. This makes the employees aware that management now knows their feelings and perceptions. Now is the time for the manager/supervisor to make it clear that he or she is sensitive to those feelings and perceptions, plans to take positive action, and plans to accommodate laboratory personnel as much as possible within the scope of company policies.

Step [D], forming quality circles or action teams, is accomplished by forming small teams among the employees (four people per team for example) and having those teams meet at some scheduled interval (perhaps weekly, with no attendance by management) to discuss employee problems and to develop suggestions and ideas that will serve to improve the overall laboratory working environment.

Step [E] allows managers and supervisors to exercise their roles as facilitators, which is their most important function as members of management. A manager or supervisor should attend the action team meetings on occasion to facilitate action. The manager or supervisor should not tell the group what to do, but rather, should assist them by providing the means (tools) that the group needs to accomplish its goal or mission and keep the group on a path that is in concert with company business objectives.

Step [F] is similar to [E] but on a larger scale. Occasionally, all employees should meet together as a group to share individual action team ideas and to be informed about business conditions and long-term plans for the laboratory.

Step [G] provides for a repeat of the satisfier/dissatisfier survey every six months to measure the progress of the action team/quality of life program and to monitor the current status of job satisfaction. Keep in mind that the action teams have been established and that the repeat survey is merely

Figure 12.2. Actual satisfiers.

1. Relations between workers.
2. Relations between managers and workers.
3. Relations between supervisors and workers.
4. Devotion to quality work and time needed to do it.
5. Willingness of fellow workers to help out.
6. Opportunity to learn.
7. Working atmosphere
8. Flexible time.
9. Coworkers.
10. Money.
11. Trusted to work independently.
12. Finishing work and moving on to something new.
13. Recognition for job well done.
14. Good communications with coworkers.
15. Having fun while working.
16. When manager or supervisor asks for my opinion.
17. When supervisor acts on a suggestion.
18. Good supervisor training, but able to work independently.
19. Good relations among coworkers.
20. Coworkers helpful and understanding.
21. Supervisor fair and straight.
22. Communications in lab good.
23. Benefits good.
24. Labs are fine and supplies pretty abundant.
25. Working in good environment under good management.
26. Flexible hours.
27. Nice people to work with.
28. Good instrumentation.
29. Understanding supervisor.
30. Ability to work independently.
31. Left alone to do my own work.
32. Some people are willing to help.
33. Workload not overwhelming.
34. Company willing to bend rules in special circumstances.
35. Good pay.
36. Good benefits.
37. Overtime hours rewarded two different ways.
38. Able to work independently.
39. Flexible hours.
40. Have good automated instrumentation.
41. Opportunity to learn.

a tune-up of the system. The ongoing data collected at six-month intervals will serve to facilitate continuous improvement in quality of life in the laboratory environment.

Step [H] calls for action team meetings to be ongoing. This approach allows employees to eventually manage themselves and encourages open communications, exchange of ideas, and an atmosphere of mutual trust between managers and analysts. When referring to the list of satisfiers and dissatisfiers in Figures 12.2 and 12.3, please note that there are very few comments related to money. Yes, money is important and it is certainly desirable and rewarding to earn a good salary, but in the long run, the main thing that holds people to their jobs is job satisfaction.

Job satisfaction will certainly maximize employee performance, and identification of people's concerns, good communications, and a degree of self-management (ownership) are major contributors.

Figure 12.3. Actual dissatisfiers.

1. Cleanliness of instruments.
2. Glassware shortage.
3. No organized system for supplies management.
4. Lack of training SOPs for instruments.
5. Too little time per instrument to learn it thoroughly.
6. Need more desk space.
7. Knowledge and experience should be better recognized.
8. Education and experience not considered for promotion.
9. Manager only allows growth of one or two workers.
10. Not enough new things to learn.
11. Not knowing where things are—feeling pressure of time limits.
12. Supervisor tells you what to do even though you know how.
13. Unpredictable need for overtime.
14. Temperature in lab uncomfortable.
15. Glassware shortage.
16. Some equipment could be more efficient.
17. Air flow in lab should be improved.
18. Overtime should be better paid, and lunch not paid.
19. Supervisor sometimes not fair.
20. Supervisor sometimes acts against interest of his own people.
21. Supervisor should not instigate to divide his own people.
22. Supervisor should clean up organic waste.
23. Supervisors should not be jealous of each other.
24. People should cooperate with each other to improve productivity.
25. Drawers containing chromatograms need cleanup and organizing.
26. Reference materials not organized.
27. Promotion.
28. Communications with boss.
29. Recognition of hard work.
30. Time of shift overlap—space constraints.
31. Requests for training and needed supplies not taken seriously.
32. Having to clean up after coworkers.
33. Unlabeled materials left in lab—lab a mess.
34. Supervisor feels his ideas are the only ideas that are worthwhile.
35. Others not working up to potential.
36. Orders left to last minute.
37. People hoard things when there is a material shortage.
38. Animosity between shifts.
40. Supervisor not listening most of the time.
41. Indecisiveness when assigning menial tasks such as cleanup.
42. Many improvements unseen or unrewarded.
43. Work not fairly distributed.
44. Supervisors play favorites.
45. Not trained well on HPLC.
46. Misunderstandings.
47. Coworkers not friendly.
48. No credit for positive acts.
49. Lab divided into two factions—need more unity.
50. Lots of politics and competition.
51. Double standard.

However, there are several other components of manager/employee interactions that are critical to overall job satisfaction. These are performance reviews, discipline, job interest, and the manager as a listener.

12.1.1.1 Performance Reviews

It is beyond the scope of this book to attempt a detailed discussion of human resource programs. Instead, the discussion of performance reviews will center on a few useful techniques that should help most laboratory managers to conduct smooth performance reviews that will leave employees motivated and feeling good about themselves. The time spent in an employee review must be private time between the manager and the employee. No interruptions of any kind should be permitted or tolerated. Find an office or conference room where the door can be closed and privacy maintained. If this is not possible on site, then find an off-site location, such as a quiet restaurant. Managers should inform their bosses that they are conducting a review and would prefer to do so without interruption.

Make the review mostly positive. If the review lasts 30 minutes for example, get the negatives out of the way in the first 5 minutes, then move on to positive achievements and plans for the future. It helps to discuss plans for the overall operation and how the employee will fit in as an important contributor. Finally, the review should be ended on a positive note. Following these simple steps, most employees will come out of their review meeting feeling good about themselves and will be motivated to improve their performance.

12.1.1.2 Discipline

Discipline is often thought of in terms of children and parents, and unfortunately, some managers treat their workers as children instead of professionals. Some unenlightened supervisors have been known to use such unfortunate phrases as "You jerk," "You idiot," "How could you be so stupid?" and so on. Everyone makes mistakes, but if spoken to in a demeaning manner, the employee will become defensive, will resent the supervisor, and might even become temporarily or even permanently less productive, not to mention any legal problems that could arise.

The following scenario, taken from experience, demonstrates an effective and diplomatic use of discipline:

> A laboratory analyst was doing a Kjeldahl determination that involved adding 50 percent caustic soda to a reaction vessel containing water. The proper technique was to pour the caustic soda down the sides of the vessel to create a layer of caustic soda below the reaction mixture, after which the vessel would be sealed and the mixture mixed to start liberation of ammonia.
>
> The analyst was observed by the laboratory manager, "dumping" the caustic into the reaction vessel instead of pouring it down the side. At this point, the manager, in anger or ignorance, could have made some negative remarks in a harsh tone of voice such as "What are you doing? What's the matter with you? What are you trying to do, blow up the lab?"

Fortunately, the manager in this case had interpersonal relationship skills and spoke to the analyst as follows:

> "Could I speak with you for a moment? I noticed that, when doing the Kjeldahl analysis, you dumped the caustic soda into the reaction vessel instead of pouring it down the side. I appreciate your efforts and know how much it means to you to be productive and to do a good job. However, I would prefer that, the next time you do a Kjeldahl, you pour the caustic down the side as the method specifies, because it is safer. By just dumping it in, you might liberate ammonia before the vessel is sealed, causing a low analytical result. I would rather have you take a little more time and do it right. Let's review the SOP together right now, and if you like, I would be more than happy to assist you the next time you run a Kjeldahl analysis."

Notice that the above conversation deals with the situation in a totally positive way. The analyst knows that he has made a potentially serious mistake and knows that the laboratory supervisor is well aware of it. But instead of being reprimanded or degraded, the analyst comes out of the situation feeling good about the constructive, positive, and helpful nature of the conversation with his supervisor, feeling that his manager is concerned about his career and wants him to succeed. Chances are, that analyst will return to the laboratory where he will do a better job and will probably not repeat his mistake. In addition, he might even help others in the laboratory avoid such errors by teaching them correct technique.

The analyst in the above example was disciplined (reprimanded) to be sure, yet the disciplinary session with the manager felt more like a training session than it did a reprimand.

In most cases, positive handling of problems will result in the problem becoming a learning experience, where one learns by one's mistakes. Where mistakes are chronically repeated, we enter the realm of "passenger removal" which was discussed in chapter 4.

12.1.1.3 Job Interest

Job interest is another part of job satisfaction that is all too often overlooked. When pressure is on to produce, a laboratory manager might be, and often is, tempted to assign work to those analysts who do a particular task best. The result is an assembly line laboratory where people are doing the same things each and every day, resulting in boredom and lack of professional growth. It is extremely important for the laboratory manager to rotate work and to cross-train analysts to be backups for each other. If only one analyst is trained on HPLC and that analyst calls in sick or gets hit by at truck, the productivity of the laboratory will suffer. Therefore, both cross-training and work rotation are extremely important in maintaining a keen job interest among workers.

In addition to the above factors, the manager must first and foremost be a good listener. The manager should have an open door policy that allows workers to vent their feelings and concerns, whether it be business or personal. Always make time to listen. Be perceived as a caring and sympathetic manager to whom a person can go to at any time with any problem, and the goal of achieving and maintaining worker loyalty, productivity, respect, and quality of work will be well served.

12.2 PLACES

Places refers to different kinds of analytical laboratories and their attributes. Individual characteristics of several major types of analytical laboratory operations will be examined, starting with the quality control laboratory.

12.2.1 The Quality Control Laboratory

QC is probably the most common type of analytical laboratory. It serves virtually every industry requiring analytical production support and is an environment to which the SPACE system is especially well suited. In the quality control environment, safety, productivity, accuracy, credibility, and education are essential to success.

In addition to the tools and techniques described throughout this work, the QC environment is particularly well suited to application of statistical quality control (SQC) as a means of providing information to the Manufacturing and Quality Assurance groups, and as a means of controlling the laboratory's cost of quality.

SQC for the laboratory, presented in chapter 7, section 7.1.6 and chapter 9, section 9.2, involves developing control samples and using statistical data on controls as a means of monitoring laboratory quality. But what about product quality? It isn't enough to do the analysis and see if specifications are being met. The QC lab needs to be involved in SQC as a means of providing data that will result in continuous quality improvement.

It is not sufficient for the Quality Control laboratory to be in control itself; QC must also take a proactive role in monitoring and reporting manufacturing process control through a process of critical statistical analysis of analytical results obtained by analysis of production samples. Statistical quality control (SQC) data on production samples generated by QC are used to monitor plant process performance. The data play an important role as a major component of annual process review as a tool for determining whether any process validation or revalidation is required.

Because QC labs see large volumes of samples, they generate sufficient data to provide good SQC analysis. As an example, look at Figures 12.4 and 12.5, which are statistical quality control charts for two analytical parameters listed in that product's release specifications. The charts give a pictorial view of how these parameters vary from batch to batch. Statistical parameters such as mean, standard deviation, and process average are shown. These statistical data allow for meaningful analysis of the process and provide invaluable information to production personnel, enabling them to look at trends and predict potential problems before they occur.

Statistical data on process parameters are also valuable for obtaining ISO-9000 certification, preferred vendor status with customers, and most of all, for getting a better understanding of plant processes which can only lead to the production of products that consistently meet specifications, because the process is predictable.

In addition, the use of SQC can have a major impact on how well a company does during an FDA inspection. SQC data can be used as the basis for retrospective validation on older products and can be used to demonstrate, both statistically and graphically, that current validated processes are in control.

Refer now to Figures 12.4 and 12.5 and their accompanying data tables for a detailed example of how to use SQC for evaluation of process data.

Figure 12.4 is an SQC chart showing a plot of assay values for 24 batches of acetaminophen (APAP) granulation. Figure 12.5 shows bulk density data for the same material (APAP granulation).

SQC can reduce the cost of quality and provide production engineers and management with valuable process feedback. Before proceeding with data analysis, a definition of terms is in order.

Review of the statistical data for APAP assays shows the granulation process for APAP to be in poor statistical control as is evidenced by a process performance index of only 0.81. The frequency distribution is skewed on the tight side (100 percent of data ± 2 sigmas). In this particular case though, the computed upper and lower control limits are tighter than the upper and lower specification limits (USL and LSL). UCL-LCL = 3.0, while USL - LSL = 4.0., and since 100 percent of all data points are within the mean ± 2 sigma, it is unlikely that this process, even though it is not in statistical control, will not yield any batches of APAP granulation that are out of spec for assay. Finally, the Ppk value is nearly equal the Pk value, indicating that the process is "center cut," i.e, the process mean and the statistical mean (90.0 vs. 90.1) are nearly identical. In the case of APAP assays, QC would report to plant personnel that, although the process is out of statistical control, there is little cause for concern, since other statistical parameters are such that a product failure is very unlikely. However, QC should encourage the plant to reduce the variation from point to point in order to get lower standard deviations, which will in turn yield a high process performance index.

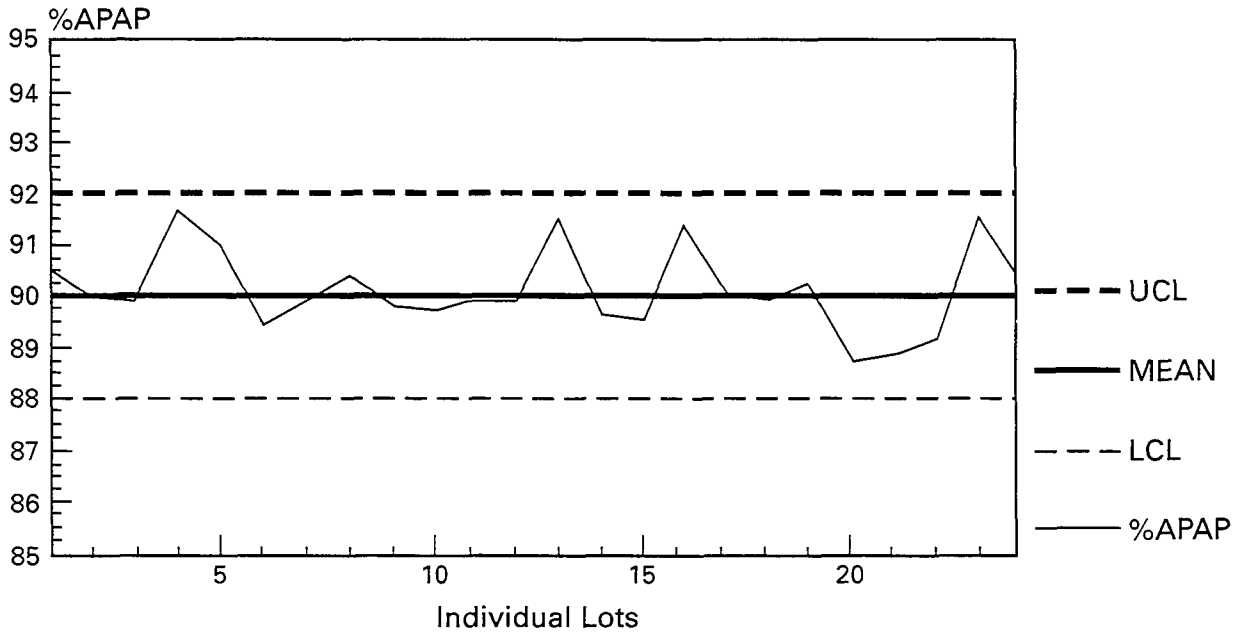
It is extremely important for the QC manager or supervisor to look at all the data and to examine all the statistical parameters when conducting an SQC evaluation of process data. The process performance index, distribution, specification ranges, and degree of centering must all be considered before any feedback is given to Manufacturing. Misinterpretation of data could have serious consequences. It is strongly recommended that every laboratory manager and supervisor take a course in basic statistics and that they become familiar with the use of control charts.

In the case of the bulk density parameter, frequency distribution is also skewed high, with 79.2 and 100 percent of the data falling within ± 1 sigma and ± 2 sigmas from the mean, respectively. The Pp value of 2.98 indicates that the process is in excellent statistical control for bulk density. Additionally, since the computed upper and lower control limits are tighter than the product specification limits for bulk density, and since it is shown that 100 percent of the data will fall between the computed upper and lower control limits, it can be suggested that this test does not need to run on a routine basis, thereby reducing the cost of quality without compromising product integrity. In this case, even though the centering is poor (the plant should be encouraged to improve this), the distribution is so tight and the process in such good statistical control that any chance of a failing result for bulk density is virtually nonexistent.

This application of SQC (using it to reduce testing), sometimes called critical point analysis, is an exciting and reliable way to reduce the cost of quality.

Here is a case where the Quality Control Laboratory has done its job, which is to control both quality and the cost of quality. If all elements of the SPACE system are in place, the laboratory itself

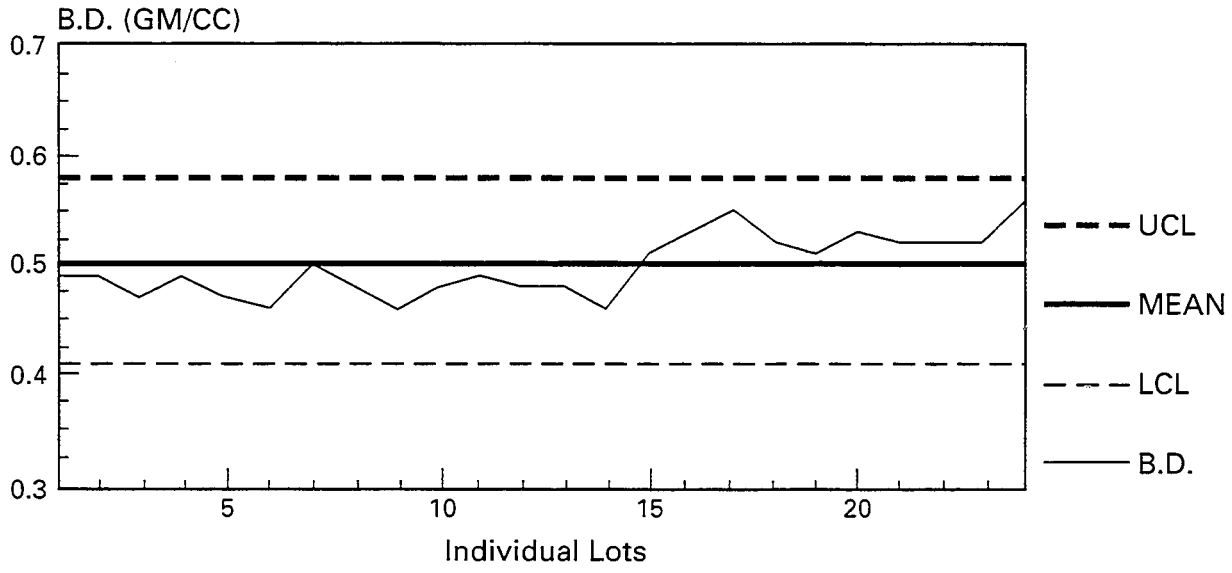
Figure 12.4. Acetaminophen granulation assay—24 consecutive batches.



Raw Data for APAP Assay Chart Figure	
BATCH NUMBER	**BULK DENSITY (g/cc)**
1	90.5
2	90.0
3	89.9
4	91.7
5	91.0
6	89.4
7	89.9
8	90.4
9	89.8
10	89.7
11	89.9
12	89.9
13	91.5
14	89.6
15	89.5
16	91.4
17	90.0
18	89.9
19	90.2
20	88.7
21	88.8
22	89.1
23	91.5
24	90.2

Statistical Data—APAP Assays	
PARAMETER	**VALUE**
Mean	90.10%
Sigma	0.82
Range	88.7–91.7%
Computed UCL	92.56%
Computed LCL	87.64%
Upper Spec USL	92.00%
Lower Spec LSL	88.00%
% Within ± 1Σ	66.70%
% Within ± 2Σ	100.00%
% Within ± 3Σ	100.00%
Pp	0.81
Ppk	0.77

Figure 12.5. Acetaminophen granulation bulk density (GM/CC)—24 consecutive batches.



Raw Data—Bulk Density (GM/CC)	
BATCH NUMBER	**BULK DENSITY (g/cc)**
1	0.49
2	0.49
3	0.47
4	0.49
5	0.47
6	0.46
7	0.50
8	0.48
9	0.46
10	0.48
11	0.49
12	0.48
13	0.48
14	0.46
15	0.51
16	0.53
17	0.55
18	0.52
19	0.51
20	0.53
21	0.52
22	0.52
23	0.52
24	0.56

Statistical Data—APAP Assays	
PARAMETER	**VALUE**
Mean	0.50
Sigma	0.03
Range	0.46–0.56
Computed UCL	0.58
Computed LCL	0.42
Upper Spec USL	0.68
% Within ± 1Σ	79.20%
% Within ± 2Σ	100.00%
% Within ± 3Σ	100.00%
Lower Spec LSL	0.38
Pp	2.98
Ppk	1.43

Figure 12.6. Definitions and concepts.

1. **Mean** Average value for a given number of data points

2. **Sigma** Standard deviation

3. **Computed LCL and UCL**

   LCL Lower Control Limit = Mean - 3 standard deviations

   UCL Upper Control Limit = Mean + 3 standard deviations

   These are what the specifications should be based on actual process data. 99.44 percent of the batches produced will fall into this range if statistical variation is normal.

4. **Pp value** Process performance index

   Pp (UCL-LCL)/6s (s = Sigma)

   Pp > 1.3 Process in good control

   Pp between 1.0 and 1.3

   Process in control but should be watched

   Pp < 1.0 Process out of control

5. **Ppk value** Process average adjusted for process performance

$$Ppk = MIN\left[\frac{USL - PA}{3s}, \frac{PA - LSL}{3s}\right]$$

   Ppk values should equal to or slightly less than that of the process performance index.

6. **Frequency Distribution**

   How individual points are distributed.

   Theoretical values for a normal distribution:

   % of data within ± 1 Sigma = 68.26

   % of data within ± 2 Sigma = 95.44

   % of data within ± 3 Sigma = 99.44

   % of data within ± 4 Sigma = 99.99

should be in control, and as such, can use its analytical results to provide reliable and valuable feedback to Manufacturing and Quality Assurance. These examples demonstrate the special responsibility that falls upon the quality control laboratory. QC groups must be the perpetual watchdogs over quality, constantly monitoring themselves as well as others.

12.2.2 R&D and Environmental Operations

Other specific laboratory operations worth mentioning besides quality control are environmental and R&D operations.

Environmental labs have strict requirements regarding documentation and quality assurance, but they also have one additional requirement known as "chain of custody," which means that the whereabouts of a sample must be accounted for at all times. For example, if a company has a permit to discharge treated wastewater into a primary waterway, it will be required to take a sample at some interval and to test for certain parameters to be sure that the water being discharged meets environmental standards set forth in that company's discharge permit. When the sample is taken, the laboratory must record who took it; the time it was collected; the time it was transferred to the lab and by whom; where it was stored, by whom; and who handled it during the course of analytical work. A full chain of custody has to be maintained. Any handling, transfer, or collection of sample must be documented. The sample's whereabouts needs to be known at all times. Sample preservation must also be documented. In addition, it must be demonstrated, that when a sample is not being used, it is securely stored to avoid tampering.

Environmental labs are regulated by the U.S. Environmental Protection Agency (EPA) and are inspected by EPA, and/or state agencies on a regular basis. The EPA also sends in blind controls on a quarterly basis to all environmental labs for testing. Consistently poor performance on these control samples can cost the environmental laboratory its certification. The environmental laboratory is included here because its requirements are at least as stringent, and perhaps even more stringent, than those imposed by FDA on pharmaceutical labs. Every pharmaceutical laboratory manager should become familiar with the basic protocols used in the environmental laboratory environment, as it will provide a different view of the world that will surely benefit the pharmaceutical laboratory manager in his or her pursuit of excellence.

The last laboratory to be examined is the R&D laboratory. The SPACE system and Tools of the Trade should be applied here as well, even though the pace of an R&D group is usually much slower and more relaxed than that of a QC operation, and an R&D group sees a different mix of samples than those submitted to control labs. R&D work is generally of an exploratory or developmental nature, and R&D chemists tend to be better trained and educated than analysts in control labs. Therefore, in R&D, a strong emphasis has to placed on professional development and vigorous interaction between colleagues. Also, since work is project oriented rather than task oriented, R&D analysts work much more independently than do control analysts. The R&D laboratory manager has to allow his or her people creative freedom and plenty of elbow room to work on their own. The manager should assign what to do, not how to do it. Analytical R&D laboratories are somewhat fortunate in that they get to think about what they are doing a little more often than do analysts in laboratories driven by the pressures of daily or hourly deadlines. Because of this, analytical R&D groups have certain responsibilities to the QC laboratories for whom they are doing methods development for example. Relationships between R&D and QC have already been touched

upon when such issues as interlaboratory efficiency matching were discussed in chapter 4. But there is still one major area of analytical R&D activity that warrants further delineation–analytical methods development.

R&D needs to design methods that can be run by QC analysts on QC equipment in a reasonable length of time. An elegant method that can only be performed by one or two chemists in the company, or that takes three days to do, might make for a nice publication, but it won't do much for QC productivity. Standard cycle times for producing products usually include the time it takes for laboratory testing. Long cycle times can cause customer delays and inefficient material control. Therefore, plant management prefers quick turnaround times by control laboratories in order to release product as quickly as possible.

One way to assure that R&D methods are suitable for the QC environment is to assign each R&D chemist to the QC laboratory for several weeks, working as a QC analyst. After working in the QC environment, the R&D chemist will not only have learned to appreciate the problems faced by QC labs, but will also be in a better position to develop methods and procedures that are suitable for the QC environment, taking into account such factors as level of skill and equipment capability. The R&D chemist who has QC exposure will tend to be more practical in his or her approach to methods development, which will result in improved productivity for the company.

A second major responsibility that lies with an R&D group is its relationship with QC/control laboratories (actually a mutual responsibility), part of which is interlaboratory efficiency matching. Refer to chapter 4 for a detailed discussion.

Other R&D responsibilities include analytical methods troubleshooting, management of control samples, transfer of technology to analytical groups such as QC, and providing backup to QC in the event of an emergency, such as interruption of labor (walkouts and strikes).

12.3 THINGS

Things refers to things that were done in actual industrial situations at a number of pharmaceutical firms. A series of individual, real-life laboratory management problems is presented in Appendix A, each of which was tackled and solved by application of the techniques presented herein. Each case is presented in the form of a PAR (Problem Action Result) statement, which gives a snapshot, yet somewhat detailed look at each case.

In order to make these cases more interesting, they are presented as a challenge to the reader. Each PAR statement is presented showing only the Problem and the Result. Blank spaces are left in between for the reader to write out the action steps needed to achieve a solution to the problem that will lead to a result similar to that shown in the PAR statement. This will serve to promote practice of problem-solving skills, and can be used as a management training tool for individuals or for workshops.

An answer key is also provided in Appendix A. Readers are encouraged to use their own knowledge and experience, plus information from this book, in developing their own action plan for a solution to the problem in each of the sample cases.

The answer key shows actions that were actually taken that lead to the desired result in each of the sample cases. After completing the PAR statement exercise, readers should compare their action plans with those used by the author. Readers should also try to identify which components of the SPACE system were applied and which Tools of the Trade were used to solve each of the sample cases.

There are no right or wrong answers to these PAR problems, there is only your solution to each problem. This author hopes that the information contained in this book will be beneficial to laboratory managers and supervisors, both in day-to-day and in long-range management of analytical laboratory operations.

The problems that are stated in the 15 PAR statements did not occur overnight. In each instance, laboratory deficiencies, whether laboratory or management related, had developed over some period of time. Regardless of how bad each situation had become, each was solved by straightforward application of the 14 Tools of the Trade as part of the SPACE system of laboratory management.

Every analytical laboratory experiences problems from time to time, but what should be avoided are "creeping" chronic problems that can evolve quickly into out of control situations. As a fellow scientific professional who has been exposed to a wide variety of experiences involving analytical laboratories, and who has enjoyed great success as a problem solver in the laboratory environment, I hope that the information contained herein will make the job of managing your analytical laboratory easier and more pleasant. After all, managing the analytical laboratory should as be plain and simple as possible.

CHAPTER

13

Wrapping It All Up: Is Your Laboratory Ready for an FDA Inspection?

13.1 CAN COMPLIANCE AND PRODUCTIVITY COEXIST?

The preceding 12 chapters have

- Defined the problems facing the analytical laboratory.
- Presented and explained the 14 Tools of the Trade needed to deal with individual components of laboratory operations.
- Demonstrated, using examples and case histories, how the SPACE system of laboratory management uses the Tools of the Trade as the basis for design and implementation of a comprehensive laboratory management plan.

All the ingredients for a well-run laboratory are in place. Using Newlabs, Inc. as an example, assume that the company has utilized the SPACE system of laboratory management, and as a result, has become an efficient, efficacious operation. Management is pleased, laboratory analysts enjoy excellent job satisfaction, and analytical data are thought to be beyond reproach.

One morning, without warning, several individuals walk into the company's reception area and announce that they are from the U.S. Food and Drug Administration (FDA), and that they have come to conduct an inspection of Newlabs, Inc. What happens next? The laboratory meets its own internal standards, but what about the FDA's standards for laboratory GMP compliance? Do compliance and productivity coexist at Newlabs, or despite the firm's best efforts, are there any regulatory deficiencies?

13.1.1 The Snapshot Approach

FDA inspections are managed by their district offices, located throughout the United States. Each district has a director, compliance personnel, and investigators. It is the investigators who carry out the actual inspections of firms that are regulated under the Food, Drug, and Cosmetic Act. As with any organization, the FDA does not have unlimited manpower, and as such, must maximize their use of labor and resources.

FDA investigators tend to use a "snapshot" approach to inspection of firms. They look at random samplings of items such as batch records, laboratory data, complaints, returned or reprocessed goods, annual reviews, validations, sanitation, and housekeeping. If all the snapshots come out good, i.e., no major deficiencies are observed or no non-compliant trends are noticed, then the inspection will be short, as will the firm's 483. On the other hand, if the snapshots are poor, revealing such items as missing batch records, lack of raw data, or samples being tested before the batch was made, then the inspection may not be so short. Investigators may take samples, call in additional specialists such as chemists and microbiologists, and may even ask for additional investigators. A poor FDA snapshot can, and usually does, cost a firm substantial time and money in design, implementation, and documentation of corrective actions. FDA investigators are not only investigators, they are first and foremost U.S. Consumer Safety Officers. Their job is to protect the American consumer by reporting violations of the laws applicable to foods, drugs (including medical devices and biologics), and cosmetics.

13.1.2 After the Inspection

After the inspection is over, the firm will have an exit interview with the investigator(s). At that time the firm will be issued a Form 483, which is a list of observations that were made by the investigator or investigators during the course of the inspection. These observations are a list of deficiencies.

The firm can respond to the 483 verbally at the exit interview or can respond in writing. If the firm chooses to respond in writing, it should be done expeditiously, usually within ten (10) days of issuance.

After a response is received, it is reviewed by the District Office's compliance personnel, after which the District Office will contact the company. Depending upon the nature of the deficiencies observed during the inspection, and whether or not these deficiencies are repeat violations or not, District Office action could range anywhere from a letter acknowledging corrective actions up to a Federal Court injunction requiring court supervised corrective actions by the firm under an agreement such as a consent decree, which can be prohibitively expensive, especially for small to medium size companies.

13.1.3 A Good Relationship With FDA

There are two kinds of relationships that a firm can have with FDA; one that is built on cooperation, or one that is adversarial. Firms that take the adversarial approach usually wind up spending a fortune on lawyers and consultants, and end up with the same result that would have been achieved by cooperating with FDA up front. Arrogance and stubbornness are poor tactics to use when dealing with the FDA. Cooperation is always the best approach. If there is a disagreement with the FDA over an issue relating to the firm's 483 or subsequent actions, these can usually be negotiated or brought to the attention of higher level FDA personnel if a dispute with the District Office cannot be resolved.

13.2 THE LABORATORY CONNECTION

One may ask, why is a discussion of FDA inspections being offered in a book on laboratory management? The answer lies in the importance of the laboratory to the overall operation of any pharmaceutical operation.

13.2.1 A Solid Foundation

The importance of laboratory compliance cannot be overstated. FDA investigators will look at a number of things that depend heavily on the laboratory data upon which they are based, such as the following:

- Product release
- In-process testing
- Raw material acceptance
- Prospective process validation
- Retrospective process validation
- Cleaning validations
- Chemistry sections of new drug applications
- Manufacturing change approvals
- Annual reviews

Any of the above items could be judged inadequate or unreliable if the analytical laboratory that generated the data supporting these items has major deficiencies that could cast doubt upon the efficacy of that data. Minor laboratory deficiencies might only result in 483 observations that can be corrected easily. Major deficiencies, such as lack of suitable method validations, no instrument calibration program, missing or suspect documentation, or disregarding failing results without proper justification, could result in far more serious actions such as recalls or seizures.

Even though a pharmaceutical firm may have all its validations and drug applications in order and may be financially successful in terms of product sales, it needs to realize that a company whose analytical laboratory is out of compliance is a company that is sitting on a crumbling foundation.

13.2.2 Regulatory Reality

The best way to avoid regulatory problems in the analytical laboratory is to have a sound understanding of how an FDA investigator will conduct an inspection of the laboratory. For the purpose of this discussion, we will return to Newlabs, Inc. where the laboratory manager has applied all of the Tools of the Trade in concert with the SPACE system of laboratory management. With this in mind, how could this laboratory have regulatory problems?

Despite the best efforts of a conscientious laboratory manager, he or she needs to realize that no one is perfect. While an ideal goal is to be in perfect compliance, this is rarely achieved, and there will usually be some questions on the part of FDA investigators concerning laboratory practices and documentation.

A realistic goal is to be in substantial compliance at all times. This means that the laboratory is making every reasonable effort to meet all GMP and GLP requirements, and that there is a management attitude that promotes good laboratory practices as well as the best interests of the end consumer. If an FDA investigator is convinced that the laboratory management and

analysts are operating in a state of substantial compliance and have an attitude that demonstrates commitment to both quality output and regulatory compliance, then that laboratory will do well during its inspection.

13.2.3 The Laboratory Inspection

During an FDA inspection of an analytical laboratory, investigators will usually determine the laboratory's quality and regulatory status by looking at sequencing. Investigators may select a number of batch records or analytical report sheets at random and trace laboratory results back to the raw data to be sure that the analytical results on those batch records or analysis sheets can be considered reliable. The sequence of events is examined in order to see if the chronology is correct. For example, looking at the sequence of events for a production batch, investigators will begin their snapshot by checking to see such things as the following:

- Were raw materials logged into the laboratory prior to beginning the batch?
- Did raw material testing begin after log in?
- Were raw materials released for use after they were tested?
- Was the batch started after raw materials were approved for use?
- Were finished product samples logged into the laboratory after the batch was completed?
- Was the finished product tested after log in?
- Was the finished product released after testing was completed?
- Are dates cited on chromatograms, spectra, notebooks, and worksheets in sequence with commencement and completion of testing?

If the answer to all of the above questions is yes, the laboratory is well on its way to having a favorable inspection. However, if problems are noted such as materials being tested before they are received or having chromatograms dated a week after release of a finished product, then the snapshot may expand into a more detailed inspection, turning up things that would not have been looked at had the laboratory passed the snapshot.

Many times discrepancies in sequencing are nothing more than typographical errors or careless entries of dates or data. Although this kind of error can usually be explained and rectified, it leaves an impression with the investigator that documentation may be sloppy. One minor incident is no cause for alarm, but if many such minor errors are noted, they will be perceived as a trend. Once a trend has been uncovered, the inspection will become far more detailed and will tend to focus on the area for which the trend was noticed, in this case, documentation. If the errors can be explained, FDA may consider the laboratory sloppy in its record keeping. If the errors cannot be explained, FDA might consider the laboratory fraudulent in its documentation practices.

Sloppiness or carelessness can damage the image of what is otherwise a well-managed laboratory. The above example is an excellent testimonial to the value of internal laboratory audits and to the use of auditors to review all laboratory data prior to publication.

After sequencing, investigators will determine whether or not

- SOPs are in place for all laboratory operations.
- SOPs are being followed as written.
- Equipment calibration has been maintained, and is current.
- Housekeeping is adequate.
- Training records are available for all analysts.
- Analytical methods are written and approved for all materials that are tested.
- Analytical methods validations are in place for all methods requiring validation.
- Stability testing has been maintained and is current and analytical methods are stability indicating.
- Notebook and worksheet practices are adequate.
- Auditing of laboratory data is adequate and current.
- Management span of authority is appropriate.
- Retesting and resampling policies are adequate.
- Failure investigation policy is adequate.
- Quality of chromatograms and spectra, and interpretation thereof are adequate.

If all of the above items actually stand up to inspection, in combination with having passed the sequencing snapshot, then that laboratory will be considered by FDA to be in substantial compliance. If the laboratory manager thinks the above items will stand up to inspection, without being certain, unexpected problems can and usually do appear.

A very common problem that can develop is created when a dead zone is spotted. For example, an investigator may notice that there was a two-day period between the time a particular piece of apparatus's calibration expired and when it was recalibrated. If the instrument passed recalibration, it is unlikely that the subject equipment had any problem during the two-day dead zone. However, had the equipment failed recalibration, all data generated on that equipment during the two-day period after expiration of the previous calibration is automatically suspect and will have to be repeated. Should repeat analyses using calibrated equipment be failing or out of specification, the result could be a product recall. In either case, the laboratory is once again thought of as sloppy or careless, and as with the previous example for sequencing, once a trend develops, the inspection becomes longer and more detailed. Other examples of dead-zones to be aware of are missing data, blank notebook pages, poor quality chromatograms, and analyst attendance records.

FDA investigators are highly trained observers who are expert in finding things that a laboratory manager would never consider, and despite that manager's best efforts and intentions, he or she could still find him or herself answering some very embarrassing questions.

For example, analyst attendance records have been mentioned as a possible dead-zone. Why? Suppose, during FDA inspection of laboratory notebooks, it is noted that analyst #1 signed his notebook page as having done the work on February 10, 1995. Analyst #1 was actually out sick on February 9, 1995, but in error, was marked as absent on February 10, 1995 (sloppy record keeping. If the FDA investigator checks attendance records for analyst #1 as part of his or her sequencing snapshot, the laboratory manager is going to have the unpleasant task of explaining how an analysis was done by someone who was not at work the day the analysis was done. This type of incident could be construed as fraud if the investigator cannot be convinced that the attendance records are in error, and even if the investigator can be convinced, he or she may look for further incidents in order to establish a trend.

An FDA laboratory inspection is always an adventure. Learn to expect the unexpected. Be prepared to defend your laboratory as a well-run organization that is in compliance by being in compliance. Know how to interact with FDA investigators, interpret their questions, and how to answer them. Maintain a sound laboratory quality assurance program such as that suggested in chapter 7, and maintain an ongoing process of self-inspection by way of both internal and external auditing, both of laboratory systems and of laboratory data.

13.3 AVOIDING UNNECESSARY PROBLEMS

Most problems with FDA investigators can be avoided by knowing how to deal with the investigators themselves and by knowing how to give your laboratory extra protection above and beyond that achieved by use of such techniques as the SPACE system of laboratory management.

13.3.1 Dealing With FDA Investigators

Many problems develop during FDA inspections simply because employees do not know what to say or how to act when confronted by an investigator. The following list of guidelines are especially useful when dealing with FDA investigators.

1. Answer all questions honestly.
2. Answer only the question being asked, never elaborate or go beyond the scope of the question.
3. Use yes and no answers whenever possible.
4. Never volunteer information.
5. When asked about specifics of your work, always reference the SOP that applies to that operation. For example, if you are working on an assay for APAP by HPLC, and an investigator asks, "What are you doing?", tell the investigator that you are doing an HPLC assay for APAP. If the investigator asks how you are doing it, simply hand him or her the SOP and say, "I do it this way." Never recite procedures from memory, always use the SOP. Even if the investigator says, "Don't you know the procedure by now?", simply respond, "Yes I do, but I always refer to the SOP for consistency of operations."
6. When performing a laboratory procedure, always have a copy of the SOP for that procedure on the bench, at the location where the work is being performed.

7. When asked to see a document or notebook page, for example, retrieve only that document. Do not give the investigator an opportunity to browse.
8. Do not let the investigator wander around without an escort. This avoids fishing expeditions.
9. Keep laboratory benches and desks free of any documents, notebooks, or loose papers. Anything an investigator sees or hears during an inspection can become part of the inspection.
10. Avoid small talk with investigators and avoid conversations of others within earshot of the investigator.
11. When an investigator asks for something, pin the investigator down to the exact specific item being requested.
12. Do not be afraid to say, "I don't know." If you are not sure of an answer, don't guess or stab at the answer. Simply say, "I don't know, but I'll get the answer for you." Guessing only gives the appearance of poor training and job knowledge.
13. Any document that is requested by an investigator should be produced as soon as possible, but no later than 30 minutes after the request. Long waits for documents may lead an investigator to suspect fraud, and he or she may even suspect that the document is not available and is being fabricated while waiting, thus the long delay in producing it.

Following the above guidelines will help move the inspection along in a smooth and professional manner. The investigator will understand that you know how to conduct yourself, and as a result, will be less likely to examine items that are not on the inspection agenda and will be less likely to overstep his or her boundaries of authority.

Guidelines 1–4 and 11 need some clarification. This is best achieved by presentation of sample dialogues that illustrate the points made in the subject guidelines.

Guidelines 1–4, 11: Wrong Dialogue

Investigator: Are the HPLCs calibrated on a regular basis?
Lab Analyst: Yes, they are. As a matter of fact, most of the equipment is calibrated regularly, except for this *one over here.* Would you like to see all the SOPs and calibration notebooks?

Investigator: Sure, let me see them. Also, could you find out which products were released using the *one over there?*
Lab Analyst: The calibration program we have now is great, but you should have seen things a year ago when the old manager was in charge. Why its a miracle that any lab results ever came out right.

Investigator: That's very interesting; could I see last year's calibration records as well?

The above conversation conducted between an FDA investigator and a lab analyst will result in that laboratory being subjected to the kind of scrutiny that could seriously damage its reputation and

credibility. The analyst elaborated on questions, volunteered information, and invited a fishing expedition by being so generous with information. The investigator only asked about HPLC calibrations and did not need to be informed about the entire calibration program and its deficiencies, nor did the investigator need to be told about the old manager's performance. These topics would more than likely never have surfaced during this inspection. Although trying to be helpful and cooperative, this analyst succeeded only in digging a grave for his or her laboratory.

By contrast, this conversation could, and should, have gone as follows:

Guidelines 1–4, 11: Correct Dialogue

Investigator: Are the HPLCs calibrated on a regular basis?
Lab Analyst: Yes

Investigator: Do you have calibration SOPs and log books?
Lab Analyst: Yes

Investigator: May I see them?
Lab Analyst: Exactly which SOP and log book do you want to look at?

Investigator: The SOP for calibration of HPLCs, and the current log book for HPLCs.
Lab Analyst: Is there a specific entry in the HPLC log book that you would like to see?

Investigator: No, I want to review the entire logbook.
Lab Analyst: The log book is very thick, are you sure I can't find a specific entry for you?

Investigator: No, I want to see the entire log book.
Lab Analyst: Certainly, I'll get the HPLC calibration SOP and the current HPLC log book for you right away.

Notice that this time, the analyst answers are short and the investigator is pinned down into stating exactly what he or she wants to see. No information was volunteered, and no elaboration of answers was given. If this type of dialogue continues, this inspection will be one where the investigator is not exposed to any information beyond what he or she specifically requests. Knowing how to interact with FDA investigators, particularly in answering questions, will avoid many unnecessary problems and will more than likely result in a shorter 483.

As with any FDA inspection, the laboratory inspection team should include a member of management who has a thorough knowledge of regulatory affairs and who can get rapid access to legal counsel if necessary.

13.3.2 Laboratory Certification Audits

Another way of avoiding unnecessary problems with FDA laboratory inspection is through the use of laboratory certification audits. These are comprehensive audits, done by an outside consultant,

that certify the laboratory, in writing, as to its state of compliance. The certification audit consists of the following elements:

- Management Systems
- Operating Procedures
- Personnel Training
- Data Accountability
- Method Validation
- Equipment
- Facilities
- Certification Documentation

With the exception of the certification documentation, all of the components of a lab certification are contained in this book. Application of the Tools of the Trade in concert with the SPACE system of laboratory management will meet lab certification requirements more than adequately.

Upon completion of the certification audit, a laboratory certification document must be generated by the person or group certifying the laboratory. The certification report should include, in addition to the findings related to the certification audit listed above, a list of training, by analyst, including the supervisor and reviewer of the training. In addition, it should include test methods in which the analysts have been trained, equipment and test on data systems on which analysts have been trained, and standard laboratory procedures that have been reviewed and found acceptable. The final certification report should be signed and dated. Since the report will be incomplete after a short period of time, due to hiring of new analysts, development of new methods and programs, and purchase of new equipment, there should be provisions for periodic updating of the certification document. A reprint of "FDA GUIDANCE ON QC LABORATORY CERTIFICATION" can be found in "The Gold Sheet," Volume 28, No. 12, December, 1994, published by F-D-C Reports, Inc.

13.4 A FINAL WORD

Surviving an FDA inspection is a never ending concern. The inspection process is an ongoing event designed to protect the public by assuring that pharmaceutical firms and pharmaceutical contract organizations engaged in activities, such as manufacturing and analytical laboratory work, are operating within the law. Whether a laboratory is a quality control lab that is part of a pharmaceutical manufacturing firm, an analytical R&D group, an independent contact lab, or a bioanalytical lab that supports bioequivalence studies, the rules are the same.

The best way to stay prepared at all times is to have a well managed laboratory whose quality assurance systems and quality of data are beyond reproach, and to stay current with regulatory affairs by way of attending meetings such as the Pharmtech Conference and seminars sponsored

by such organizations as the American Association of Pharmaceutical Scientists (AAPS) or the American Society for Quality Control (ASQC), and by reading such publications as the Federal Register, The Gold Sheet, and FDA Guidelines dealing with validation and laboratory inspections and guidelines dealing with the International Conference on Harmonisation.

A well managed, well informed laboratory will not only do well in the area of productivity and efficiency, but will manage to succeed in the elusive task of making productivity and compliance coexist in the analytical laboratory.

REFERENCES

The Gold Sheet, December 1994, Chevy Chase: F-D-C Reports, Inc.

APPENDIX A: CASE STUDIES

CASE #1

PROBLEM:

Storytelling Syndrome has caused inconsistencies in operations.

ACTION:

RESULT:

Consistency of operations was restored with resulting increase in productivity and improved communication.

CASE #2

PROBLEM:

Teacher's Pet Syndrome is out of control.

ACTION:

RESULT:

1. Greater productivity because of less repeat work.
2. Better FDA inspections—less bad data to explain.
3. Happier workers—no more pressure to produce at any cost.

CASE #3

PROBLEM:

Backlog in QC due to audit logjam.

ACTION:

RESULT:

1. Audit time reduced by 80–90 percent because notebook references and transcriptions were eliminated, and because the supervisor had time to do supervisory work, including review and audit of data.
2. Bullet-proofed FDA inspection of lab records; no notebooks to criticize, no opportunity to browse. FDA only sees data for *that* batch, most of which is preprinted and not subject to error.
3. Increased efficiency of chemists by virtue of not having to fill out notebook pages.

CASE #4

PROBLEM:

Sample backlog every Monday morning—workers refused overtime. Lab was unionized.

ACTION:

RESULT:

1. Reduction or elimination of Monday-morning backlog because lab resources, particularly GCs and HPLCs, are now utilized seven days per week. Work is distributed evenly throughout the month.
2. Labor costs reduced.

CASE #5

PROBLEM:

Laboratory extremely inefficient.

ACTION:

RESULT:

1. Gross improvement in efficiency and awareness on the part of lab management as to current status of all activities.

CASE #6

PROBLEM:

Poor housekeeping and high accident rate.

ACTION:

RESULT:

1. Zero accidents and better attitude about the ergonomics of the workplace.

CASE #7

PROBLEM:

Analytical laboratory had a poor QA program.

ACTION:

RESULT:

1. High confidence in analytical data.
2. Tools now available for demonstrating efficacy to regulatory agencies and to management.
3. Less repeat work because of more confidence in data that are generated.
4. Better compliance.

CASE #8

PROBLEM:

Competence of workers was suspect.

ACTION:

RESULT:

1. Productivity and accuracy, as well as morale among competent analysts, improved markedly.

NOTE: Workers are often discouraged when they see others around them who are incompetent or lazy, getting the same pay and other considerations as the "real" performers. Showing the performers or the movers and shakers that management recognizes individual performance, both good and bad, will tend to improve the morale of good employees.

CASE #9

PROBLEM:

Laboratory department had an extremely poor training program.

ACTION:

RESULT:

1. Better educated, better informed analysts, and better regulatory position due to documented training.
2. The use of practice samples reduced the amount of bad data that needed to be explained.

CASE #10

PROBLEM:

QC testing lags were causing delays, and the cost of testing was out of control.

ACTION:

RESULT:

1. Increase in QC efficiency and reduced testing as a result of confidence in analytical data, resulting in a $60,000 per year reduction in the cost of testing.

CASE #11

PROBLEM:

For a major product, the plant was submitting 6 samples per shift, plus a composite of the 6 on each shift, for a total of 21 samples per day, each of which received full monograph testing. How could the amount of testing be reduced?

ACTION:

RESULT:

1. Testing on this product was reduced from 21 samples per day to 3 samples per day, resulting in a labor savings of 1500 man hours per year.

CASE #12

PROBLEM:

Firm had poor FDA inspections and was in danger of being shut down. The Teacher's Pet syndrome was widespread throughout the QC laboratory. Cheating and fabrication of data were suspected.

ACTION:

RESULT:

1. The next FDA inspection was favorable, with only four minor 483 observations. In addition, productivity increased, credibility was restored, and a previously high turnover rate was virtually eliminated.

CASE #13

PROBLEM:

Laboratory geography and technology were poor, and operations were extremely inefficient. Credibility was also poor, and productivity was so low that the lab could not meet the needs of the plant.

ACTION:

RESULT:

1. Efficiency and productivity doubled, skills of analysts markedly improved, and credibility was restored.
2. The laboratory was able to keep up with plant work load for the first time ever.

CASE #14

PROBLEM:

The firm had no process validation data for their principal products; however, there were analytical data preserved that spanned several years of production. The lab was audited by an outside consultant and was found to be totally out of compliance, putting all analytical test results in question. The task was to guarantee the efficacy of the older analytical data and to produce validation documents for all principal products.

ACTION:

RESULT:

1. The laboratory was brought into compliance and retrospective validation documents were produced for all principal products.

CASE #15

PROBLEM:

The laboratory director of a large contract laboratory was experiencing difficulty in maintaining good relations with managers who reported to him and in maintaining good relationships between the managers themselves. Cliques had formed in the lab and chemists were distrustful of management.

ACTION:

RESULT:

1. This contract laboratory is now running smoothly with no major personnel problems. Teamwork and communications have improved dramatically.

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #1

ACTION:

1. SOP review by each chemist and supervisor every six months was instituted, with documentation of that review in the form of a training attendance sheet.
2. Total-immersion supervision started, which consisted of supervisors being "on the floor," actively watching what is going on, asking questions of the chemists and constantly challenging the activities of each chemist as a means of getting the kind of feedback that allows the chemist to explain what he or she is doing, resulting in strong reinforcement of training.
3. Supervisors started reviewing SOPs with each other on a regular basis to ensure consistency among themselves.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #2

ACTION:

1. Employees were encouraged to slow down and do it right the first time.
2. Supervision was trained to tell the people what it is by clearly defining expectations. Supervision was also made aware that if people know what to do, they will do it. If not, they will make mistakes. Additional training and total-immersion supervision were implemented.
3. A mind set was developed among management and supervision that it is okay to push people to their limits, but not beyond to the point of errors, shortcuts, and job dissatisfaction.
4. The principle of accuracy before speed was instilled in all employees, because accuracy comes first. Speed will follow naturally with experience.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #3

ACTION:

1. Went to notebookless system by converting to worksheets
2. Worksheets were coded with a unique ID number and issued by QA to avoid unauthorized duplication.
3. Increased available supervisory review time by going to total-immersion supervision

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #4

ACTION:

1. Staggered workdays to match schedule of manufacturing.
2. 1/3 of the chemists remained on a Monday–Friday schedule as their normal workweek, 1/3 of the chemists were assigned to work Tuesday–Saturday, and 1/3 of the chemists were assigned to work Sunday–Thursday as their normal workweek. Rotation of shifts distributed work hours fairly.
3. Shifts were assigned by asking for volunteers in order of seniority. Unfilled slots were assigned on the basis of reverse seniority. The Union could not dispute actions taken since the bargaining agreement stated that the company had the right to set hours of work. Since the assigned shifts were regularly scheduled 40-hour weeks, they were considered normal working hours as opposed to overtime.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #5

ACTION:

1. Task-oriented workload implemented.
2. Arranged lab geography so that most tests were done without the chemist having to move outside of a 10-foot radius of the work area. For example, balances, reagents, and titrators for wet tests were located in the same area.
3. Supervisors adopted the use of the accelerated problem-solving loop.
4. Support systems were instituted.
5. Computer tracking of workload went on-line.
6. HPLC column reduction by R&D—methods from R&D were limited to 2–4 column types, allowing QC to have instruments (systems) assigned to groups of products.
7. Structured workload assignments; posted work assignments for the day, which were displayed on laboratory bulletin board.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #6

ACTION:

1. Internal safety program adopted.
2. Compliance with the OSHA Laboratory Standard was implemented.
3. Time allocation for cleanup implemented. Each day, work stopped 10 minutes early to allow for a cleanup period. In addition, once a week, a 30-minute cleanup period was used.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #7

ACTION:

1. Instituted documented system of calibration and maintenance, document control and monitoring, and proper labeling of standards, solutions, and reagents.
2. Put in control samples with every analysis as an additional check on analytical systems.
3. Use of blind controls was introduced into each laboratory as a means of checking the quality of all data, both "good" and "bad." These samples would be submitted with dummy batch numbers and the results used to evaluate the quality of data, systems, and chemists.
4. Developed SQC charts for analytical data for each major product that will show process capability and whether a process is center-cut or skewed towards one end of the spec range for any parameter.
5. Developed SQC charts for analytical standards to track capability of analytical method. Is the method in control?
6. Audit of lab by QA group and by outside consultants was instituted.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #8

ACTION:

1. A series of skills evaluation exercises in conjunction with data from control samples was used to evaluate all lab analysts and supervisors.
2. Those classified as passengers were removed from the laboratory environment.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #9

ACTION:

1. A schedule of in-house technical seminars was designed and implemented.
2. Documentation (computerized) set up for training.
3. Training was designed to focus on new SOPs and reinforcement of existing ones.
4. Supervisors were taught how to follow up on seminars with reinforcement at the bench level, letting the chemist tell the supervisor what he or she has learned.
5. On-the-fly training was documented.
6. Policy established where new chemists should be trained for some period (4–6 weeks) prior to doing "live" samples.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #10

ACTION:

1. QC operations audited and deficiencies identified.
2. SQC charts developed for all major analytical tests.
3. Parallel workload implemented.
4. Support systems were put in place.
5. Total-immersion supervision was implemented.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #11

ACTION:

1. SQC charts of individual analyses versus analyses of shift composites showed no difference in statistical parameters. Because the composites yielded the same process information as the individual analyses, analysis of individual samples was eliminated without any significant risk of product failure due to reduced testing.
2. A policy was established, where if one lot of material did fail, normal testing would be resumed until 10 consecutive lots passed, after which reduced testing would resume.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #12

ACTION:

1. In this situation, virtually all the Tools of the Trade were applied in order to improve laboratory operations, particularly in the area of compliance. A 10-month improvement program included sweeping changes in personnel, addition of new technology, going to self-contained paperwork, cross-training, computerization of sample tracking, and an intense training program dealing with safety and compliance issues, proper documentation, calibration of equipment, and validation of analytical methods.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #13

ACTION:

1. Laboratory equipment was upgraded or replaced in order to achieve current state of the art.
2. Equipment was arranged in such a manner that analysts could perform analytical tasks with a minimum of physical travel.
3. Samples with similar tests were grouped and run in parallel.
4. A vigorous quality assurance program was introduced that included the use of both controls and blind controls.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #14

ACTION:

1. All lab equipment was factory serviced and calibrated.
2. In-house calibration program established (SOPs and Training).
3. Once calibrations were done, random numbers of retention sample were tested and the analytical results compared to those originally obtained. The number of retention sample selected was $\sqrt{n}+1$ of the total number of retention samples. For example, 24 lots would require a retention sample size of six (6).
4. Once the analytical results of retention versus original was shown to be equivalent, then the original analytical results were accepted as valid.
5. SQC charts were plotted for each specification parameter for all principal products, using original analytical data.
6. SQC data showed each product process to be in control, and that each would consistently produce product that meets specifications. The SQC data were then used to generate retrospective validation reports for all principal products.
7. Existing chemists were terminated for poor performance and non-compliance with Current Good Manufacturing Practices.
8. New technical staff was hired. Each new analyst was properly trained in SOPs, analytical methods, and safety/housekeeping.

READER NOTES:

PROBLEM–ACTION–RESULT STATEMENT ANSWER KEY—ACTIONS USED

CASE #15

ACTION:

1. The laboratory director and each of his managers were interviewed privately and asked to give their honest opinions as to the state of the laboratory and the nature of the relationships they had with bosses and colleagues.
2. The rank and file analysts were given the satisfier/dissatisfier survey. Their feelings were consistent with those of their managers.
3. Job satisfiers and dissatisfiers were discussed with the laboratory director and with the president of the company. An evaluation of the laboratory director as an effective leader was also discussed in private with the company president. The main problem was the laboratory director.
4. An action plan was formulated to help the laboratory director modify and improve his management style so as to motivate people rather than making them resentful towards him.
5. The action in this case was to accept the laboratory director's resignation, as he recognized that he could not make the adjustments necessary to succeed in this particular organization.

READER NOTES:

APPENDIX B

FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories—July 1993

IMPORTANT INFORMATION

This is a reproduction of an official document. The contents of the original have not been changed in any way. Please note that, while this document represents the best possible reproduction of the original, it may reveal the graphic limitations of the source document.

GUIDE TO INSPECTIONS OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

July, 1993

1. INTRODUCTION

The pharmaceutical quality control laboratory serves one of the most important functions in pharmaceutical production and control. A significant portion of the CGMP regulations (21 CFR 211) pertain to the quality control laboratory and product testing. Similar concepts apply to bulk drugs.

This inspection guide supplements other inspectional information contained in other agency inspectional guidance documents. For example, Compliance Program 7346.832 requiring pre-approval NDA/ANDA inspections contains general instructions to conduct product specific NDA/ANDA inspection audits to measure compliance with the applications and CGMP requirements. This includes pharmaceutical laboratories used for in-process and finished product testing.

2. OBJECTIVE

The specific objective will be spelled out prior to the inspection. The laboratory inspection may be limited to specific issues, or the inspection may encompass a comprehensive evaluation of the laboratory's compliance with CGMP's. As a minimum, each pharmaceutical quality control laboratory should receive a comprehensive GMP evaluation each two years as part of the statutory inspection obligation.

In general these inspections may include

-- the specific methodology which will be used to test a new product

-- a complete assessment of laboratory's conformance with GMP's

-- a specific aspect of laboratory operations

3. INSPECTION PREPARATION

FDA Inspection Guides are based on the team inspection approach and our inspection of a laboratory is consistent with this concept. As part of our effort to achieve uniformity and consistency in laboratory inspections, we expect that complex, highly technical and specialized testing equipment, procedures and data manipulations, as well as scientific laboratory operations will be evaluated by an experienced laboratory analyst with specialized knowledge in such matters.

District management makes the final decision regarding the assignment of personnel to inspections. Nevertheless, we expect investigators, analysts and others to work as teams and to advise management when additional expertise is required to complete a meaningful inspection.

Team members participating in a pre-approval inspection must read and be familiar with Compliance Program 7346.832, Pre-Approval Inspections/Investigations. Relevant sections of the NDA or ANDA should be reviewed prior to the inspection; but if the application is not available from any other source, this review will have to be conducted using the company's copy of the application.

Team members should meet, if possible, prior to the inspection to discuss the approach to the inspection, to define the roles of the team members, and to establish goals for completion of the assignment. Responsibilities for development of all reports should also be established prior to the inspection. This includes the preparation of the FDA 483.

The Center for Drug Evaluation and Research (CDER) may have issued deficiency letters listing problems that the sponsor must correct prior to the approval of NDA/ANDA's and supplements. The inspection team is expected to review such letters on file at the district office, and they are expected to ask the plant for access to such letters. The team should evaluate the replies to these letters to assure that the data are accurate and authentic. Complete the inspection even though there has been no response to these letters or when the response is judged inadequate.

4. INSPECTION APPROACH

A. General

In addition to the general approach utilized in a drug CGMP inspection, the inspection of a laboratory requires the use of observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with CGMP's and to specifically carry out the commitments in an application or DMF. When conducting a comprehensive inspection of a laboratory, all aspects of the laboratory operations will be evaluated.

Laboratory records and logs represent a vital source of information that allows a complete overview of the technical ability of the staff and of overall quality control procedures. SOPs should be complete and adequate and the operations of the laboratories should conform to the written procedures. Specifications and analytical procedures should be suitable and, as applicable, in conformance with application commitments and compendial requirements.

Evaluate raw laboratory data, laboratory procedures and methods, laboratory equipment, including maintenance and calibration, and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with CGMP regulations.

Examine chromatograms and spectra for evidence of impurities, poor technique, or lack of instrument calibration.

Most manufacturers use systems that provide for the investigation of laboratory test failures. These are generally recorded in some type of log. Ask to see results of analyses for lots of product that have failed to meet specifications and review the analysis of lots that have been retested, rejected, or reworked. Evaluate the decision to release lots of product when the laboratory results indicate that the lot failed to meet specifications and determine who released them.

B. Pre-Approval

Documents relating to the formulation of the product, synthesis of the bulk drug substance, product specifications, analysis of the product, and others are examined during the review process in headquarters. However, these reviews and evaluations depend on accurate and authentic data that truly represents the product.

Pre-approval inspections are designed to determine if the data submitted in an application are authentic and accurate and if the procedures listed in the application were actually used to produce the data contained in the application. Additionally, they are designed to confirm that plants (including the quality control laboratory) are in compliance with CGMP regulations.

The analytical sections of drug applications usually contain only test results and the methods used to obtain them. Sponsors are not required to file all the test data because such action would require voluminous submissions and would often result in filing redundant information. Sponsors may deliberately or unintentionally select and report data showing that a drug is safe and effective and deserves to be approved. The inspection team must decide if there is valid and scientific justification for the failure to report data which demonstrates the product failed to meet its predetermined specifications.

Coordination between headquarters and the field is essential for a complete review of the application and the plant. Experienced investigators and analysts may contact the review chemist (with appropriate supervisory concurrence) when questions concerning specifications and standards arise.

Inspections should compare the results of analyses submitted with results of analysis of other batches that may have been produced. Evaluate the methods and note any exceptions to the procedures or equipment actually used from those listed in the application and confirm that it is the same method listed in the application. The analyst is expected to evaluate raw laboratory data for tests performed on the test batches (biobatches and clinical batches) and to compare this raw data to the data filed in the application.

5. FAILURE (OUT-OF-SPECIFICATION) LABORATORY RESULTS

Evaluate the company's system to investigate laboratory test

failures. These investigations represent a key issue in deciding whether a product may be released or rejected and form the basis for retesting, and resampling.

In a recent court decision the judge used the term "out-of-specification" (OOS) laboratory result rather than the term "product failure" which is more common to FDA investigators and analysts. He ruled that an OOS result identified as a laboratory error by a failure investigation or an outlier test[1], or overcome by retesting[2] is not a product failure. OOS results fall into three categories:

-- laboratory error
-- non-process related or operator error
-- process related or manufacturing process error

A. LABORATORY ERRORS

Laboratory errors occur when analysts make mistakes in following the method of analysis, use incorrect standards, and/or simply miscalculate the data. Laboratory errors must be determined through a failure investigation to identify the cause of the OOS. Once the nature of the OOS result has been identified it can be classified into one of the three categories above. The inquiry may vary with the object under investigation.

B. LABORATORY INVESTIGATIONS

The exact cause of analyst error or mistake can be difficult to determine specifically and it is unrealistic to expect that analyst error will always be determined and documented. Nevertheless, a laboratory investigation consists of more than a retest. The inability to identify an error's cause with confidence affects retesting procedures, not the investigation inquiry required for the initial OOS result.

The firm's analyst should follow a written procedure, checking off each step as it is completed during the analytical procedure. We expect laboratory test data to be recorded directly in notebooks; use of scrap paper and loose paper must be avoided. These common sense measures enhance the accuracy and integrity of data.

Review and evaluate the laboratory SOP for product failure investigations. Specific procedures must be followed when single and multiple OOS results are investigated. For the single OOS result the investigation should include the following steps and these inquiries must be conducted before there is a retest of the sample:

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[1] The court provided explicit limitations on the use of outlier tests and these are discussed in a later segment of this document

[2] The court ruled on the use of retesting which is covered in a later segment of this document.

- the analyst conducting the test should report the OOS result to the supervisor
- the analyst and the supervisor should conduct an informal laboratory investigation which addresses the following areas:

    1. discuss the testing procedure
    2. discuss the calculation
    3. examine the instruments
    4. review the notebooks containing the OOS result

An alternative means to invalidate an initial OOS result, provided the failure investigation proves inconclusive, is the "outlier" test. However, specific restrictions must be placed on the use of this test.

1. Firms cannot frequently reject results on this basis
2. The USP standards govern its use in specific cases only.
3. The test cannot be used for chemical testing results[3]
4. It is never appropriate to utilize outlier tests for a statistically based test, i.e. content uniformity and dissolution.

Determine if the firm uses an outlier test and evaluate the SOP.

Determine that a full scale inquiry has been made for multiple OOS results. This inquiry involves quality control and quality assurance personnel in addition to laboratory workers to identify exact process or non process related errors.

When the laboratory investigation is inconclusive (reason for the error is not identified) the firm:

1. Cannot conduct 2 retests and base release on average of three tests
2. Cannot use outlier test in chemical tests
3. Cannot use a re-sample to assume a sampling or preparation error
4. Can conduct a retest of different tablets from the same sample when a retest is considered appropriate (see criteria elsewhere)

C. FORMAL INVESTIGATIONS

Formal investigations extending beyond the laboratory must follow an outline with particular attention to corrective action. The company must:

1. State the reason for the investigation
2. Provide summation of the process sequences that may have caused the problem

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[3] An initial content uniformity test was OOS followed by a passing retest. The initial OOS result was claimed the result of analyst error based on a statistical evaluation of the data. The court ruled that the use of an outlier test is inappropriate in this case.

3. Outline corrective actions necessary to save the batch and prevent similar recurrence
4. List other batches and products possibly affected, the results of investigation of these batches and products, and any corrective action. Specifically:

    - o examine other batches of product made by the errant employee or machine
    - o examine other products produced by the errant process or operation

5. Preserve the comments and signatures of all production and quality control personnel who conducted the investigation and approved any reprocessed material after additional testing

D. INVESTIGATION DOCUMENTATION

Analyst's mistakes, such as undetected calculation errors, should be specified with particularity and supported by evidence. Investigations along with conclusions reached must be preserved with written documentation that enumerates each step of the investigation. The evaluation, conclusion and corrective action, if any, should be preserved in an investigation or failure report and placed into a central file.

E. INVESTIGATION TIME FRAMES

All failure investigations should be performed within 20 business days of the problem's occurrence and recorded and written into a failure or investigation report.

6. PRODUCT FAILURES

An OOS laboratory result can be overcome (invalidated) when laboratory error has been documented. However, non-process and process related errors resulting from operators making mistakes, equipment (other than laboratory equipment) malfunctions, or a manufacturing process that is fundamentally deficient, such as an improper mixing time, represent product failures.

Examine the results of investigations using the guidance in section 5 above and evaluate the decision to release, retest, or rework products.

7. RETESTING

Evaluate the company's retesting SOP for compliance with scientifically sound and appropriate procedures. A very important ruling in one recent court decision sets forth a procedure to govern the retesting program. This district court ruling provides an excellent guide to use in evaluating some aspects of a pharmaceutical laboratory, but should not be considered as law, regulation or binding legal precedent. The court ruled that a firm should have a predetermined testing procedure and it should

consider a point at which testing ends and the product is evaluated. If results are not satisfactory, the product is rejected.

Additionally, the company should consider all retest results in the context of the overall record of the product. This includes the history of the product[4], type of test performed, and in-process test results. Failing assay results cannot be disregarded simply on the basis of acceptable content uniformity results.

The number of retests performed before a firm concludes that an unexplained OOS result is invalid or that a product is unacceptable is a matter of scientific judgment. The goal of retesting is to isolate OOS results but retesting cannot continue ad infinitum.

In the case of nonprocess and process-related errors, retesting is suspect. Because the initial tests are genuine, in these circumstances, additional testing alone cannot contribute to product quality. The court acknowledged that some retesting may precede a finding of nonprocess or process-based errors. Once this determination is made, however, additional retesting for purposes of testing a product into compliance is not acceptable.

For example, in the case of content uniformity testing designed to detect variability in the blend or tablets, failing and non-failing results are not inherently inconsistent and passing results on limited retesting do not rule out the possibility that the batch is not uniform. As part of the investigation firms should consider the record of previous batches, since similar or related failures on different batches would be a cause of concern.

Retesting following an OOS result is ruled appropriate only after the failure investigation is underway and the failure investigation determines in part whether retesting is appropriate. It is appropriate when analyst error is documented or the review of analyst's work is "inconclusive" , but it is not appropriate for known and undisputed non-process or process related errors.

The court ruled that retesting:

- must be done on the same, not a different sample
- may be done on a second aliquot from the same portion of the sample that was the source of the first aliquot
- may be done on a portion of the same larger sample previously collected for laboratory purposes

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[4] The court ordered a recall of one batch of product on the basis of an initial content uniformity failure and no basis to invalidate the test result and on a history of content uniformity problems with the product.

8. RESAMPLING

Firms cannot rely on resampling[5] to release a product that has failed testing and retesting unless the failure investigation discloses evidence that the original sample is not representative or was improperly prepared.

Evaluate each resampling activity for compliance with this guidance.

9. AVERAGING RESULTS OF ANALYSIS

Averaging can be a rational and valid approach when the object under consideration is total product assay, but as a general rule this practice should be avoided[6] because averages hide the variability among individual test results. This phenomenon is particularly troubling if testing generates both OOS and passing individual results which when averaged are within specification. Here, relying on the average figure without examining and explaining the individual OOS results is highly misleading and unacceptable.

Content uniformity and dissolution results never should be averaged to obtain a passing value.

In the case of microbiological turbidimetric and plate assays an average is preferred by the USP. In this case, it is good practice to include OOS results in the average unless an outlier test (microbiological assays) suggests the OOS is an anomaly.

10. BLEND SAMPLING AND TESTING

The laboratory serves a vital function in blend testing which is necessary to increase the likelihood of detecting inferior batches. Blend uniformity testing cannot be waived in favor of total reliance on finished product testing because finished product testing is limited.

One court has ruled that sample size influences ultimate blend test results and that the sample size should resemble the dosage size. Any other practice would blur differences in portions of the blend and defeat the object of the test. If a sample larger than the unit must be taken initially, aliquots which resemble the dosage size should be carefully removed for the test, retests, and reserve samples. Obviously, the initial larger sample should not be subjected to any additional mixing or manipulation prior to removing test aliquots as this may obscure non-homogeneity.

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[5] The court ordered the recall of one batch of product after having concluded that a successful resample result alone cannot invalidate an initial OOS result.

[6] The court ruled that the firm must recall a batch that was released for content uniformity on the basis of averaged test results.

Multiple individual blend uniformity samples taken from different areas cannot be composited. However when variation testing is not the object of assay testing, compositing is permitted.

If firms sample product from sites other than the blender, they must demonstrate through validation that their sampling technique is representative of all portions and concentrations of the blend. This means that the samples must be representative of those sites that might be problems; e.g. weak or hot spots in the blend.

11. MICROBIOLOGICAL

The review of microbiological data on applicable dosage forms is best performed by the microbiologist (analyst). Data that should be reviewed include preservative effectiveness testing, bioburden data, and product specific microbiological testing and methods.

Review bioburden (before filtration and/or sterilization) from both an endotoxin and sterility perspective. For drug substance labs evaluate methods validation and raw data for sterility, endotoxin testing, environmental monitoring, and filter and filtration validation. Also, evaluate the methods used to test and establish bioburdens.

Refer to the Microbiological Inspection Guide for additional information concerning the inspection of microbiological laboratories.

12. SAMPLING

Samples will be collected on pre-approval inspections. Follow the sampling guidelines in CP 7346.832, Part III, pages 5 and 6.

13. LABORATORY RECORDS AND DOCUMENTATION

Review personal analytical notebooks kept by the analysts in the laboratory and compare them with the worksheets and general lab notebooks and records. Be prepared to examine all records and worksheets for accuracy and authenticity and to verify that raw data are retained to support the conclusions found in laboratory results.

Review laboratory logs for the sequence of analysis versus the sequence of manufacturing dates. Test dates should correspond to the dates when the sample should have been in the laboratory. If there is a computer data base, determine the protocols for making changes to the data. There should be an audit trail for changes to data.

We expect raw laboratory data to be maintained in bound, (not loose or scrap sheets of paper), books or on analytical sheets for which there is accountability, such as prenumbered sheets. For most of those manufacturers which had duplicate sets of records or "raw

data", non-numbered loose sheets of paper were employed. Some companies use discs or tapes as raw data and for the storage of data. Such systems have also been accepted provided they have been defined (with raw data identified) and validated.

Carefully examine and evaluate laboratory logs, worksheets and other records containing the raw data such as weighings, dilutions, the condition of instruments, and calculations. Note whether raw data are missing, if records have been rewritten, or if correction fluid has been used to conceal errors. Results should not be changed without explanation. Cross reference the data that has been corrected to authenticate it. Products cannot be "tested into compliance" by arbitrarily labeling out-of-specification lab results as "laboratory errors" without an investigation resulting in scientifically valid criteria.

Test results should not have been transcribed without retention of the original records, nor should test results be recorded selectively. For example, investigations have uncovered the use of loose sheets of paper with subsequent selective transcriptions of good data to analyst worksheets and/or workbooks. Absorbance values and calculations have even been found on desk calendars.

Cut charts with injections missing, deletion of files in direct data entry systems, indirect data entry without verification, and changes to computerized programs to override program features should be carefully examined. These practices raise questions about the overall quality of data.

The firm should have a written explanation when injections, particularly from a series are missing from the official work-sheets or from files and are included among the raw data. Multiple injections recorded should be in consecutive files with consecutive injection times recorded. Expect to see written justification for the deletion of all files.

Determine the adequacy of the firm's procedures to ensure that all valid laboratory data are considered by the firm in their determination of acceptability of components, in-process, finished product, and retained stability samples. Laboratory logs and documents when cross referenced may show that data has been discarded by company officials who decided to release the product without a satisfactory explanation of the results showing the product fails to meet the specifications. Evaluate the justification for disregarding test results that show the product failed to meet specifications.

14. LABORATORY STANDARD SOLUTIONS

Ascertain that suitable standards are being used (i.e. in-date, stored properly). Check for the reuse of stock solutions without assuring their stability. Stock solutions are frequently stored in the laboratory refrigerator. Examine the laboratory refrigerators for these solutions and when found check for appropriate identification. Review records of standard solution preparation to assure complete and accurate documentation. It is highly unlikely

that a firm can "accurately and consistently weigh" to the same microgram. Therefore data showing this level of standardization or pattern is suspect and should be carefully investigated.

15. METHODS VALIDATION

Information regarding the validation of methods should be carefully evaluated for completeness, accuracy and reliability. In particular, if a compendial method exists, but the firm chooses to use an alternate method instead, they must compare the two and demonstrate that the in-house method is equivalent or superior to the official procedure. For compendial methods firms must demonstrate that the method works under the actual conditions of use.

Methods can be validated in a number of ways. Methods appearing in the USP are considered validated and they are considered validated if part of an approved ANDA. Also a company can conduct a validation study on their method. System suitability data alone is insufficient for and does not constitute method validation.

In the review of method validation data, it is expected that data for repetitive testing be consistent and that the varying concentrations of test solutions provide linear results. Many assay and impurity tests are now HPLC, and it is expected that the precision of these assays be equal or less than the RSD's for system suitability testing. The analytical performance parameters listed in the USP XXII, <1225>, under the heading of Validation of Compendial Methods, can be used as a guide for determining the analytical parameters (e.g., accuracy, precision, linearity, ruggedness, etc.) needed to validate the method.

16. EQUIPMENT

Laboratory equipment usage, maintenance, calibration logs, repair records, and maintenance SOPs also should be examined. The existence of the equipment specified in the analytical methods should be confirmed and its condition noted. Verify that the equipment was present and in good working order at the time the batches were analyzed. Determine whether equipment is being used properly.

In addition, verify that the equipment in any application was in good working order when it was listed as used to produce clinical or biobatches. One would have to suspect the data that are generated from a piece of equipment that is known to be defective. Therefore, continuing to use and release product on the basis of such equipment represents a serious violation of CGMP's.

17. RAW MATERIAL TESTING

Some inspections include the coverage of the manufacturer of the drug substance. The safety and efficacy of the finished dosage

form is largely dependent on the purity and quality of the bulk active drug substance. Examine the raw data reflecting the analysis of the drug substance including purity tests, charts, etc.

Check the impurity profiles of the BPC used in the biobatch and clinical production batches to determine if it is the same as that being used to manufacture full scale production batches. Determine if the manufacturer has a program to audit the certificate of analysis of the BPC, and, if so, check the results of these tests. Report findings where there is substantial difference in impurity profiles and other test results.

Some older compendial methods may not be capable of detecting impurities as necessary to enable the control of the manufacturing process, and newer methods have been developed to test these products. Such methods must be validated to ensure that they are adequate for analytical purposes in the control and validation of the BPC manufacturing process. The drug substance manufacturer must have complete knowledge of the manufacturing process and the potential impurities that may appear in the drug substance. These impurities cannot be evaluated without a suitable method and one that has been validated.

Physical tests such as particle size for raw materials, adhesion tests for patches, and extrusion tests for syringes are essential tests to assure consistent operation of the production and control system and to assure quality and efficacy. Some of these tests are filed in applications and others may be established by the protocols used to manufacture the product. The validation of methods for such tests are as important as the test for chemical attributes.

Physical properties tests often require the use of unique equipment and protocols. These tests may not be reproducible in other laboratories, therefore, on site evaluation is essential.

18. IN PROCESS CONTROLS AND SPECIFICATIONS

Evaluate the test results from in-process tests performed in the production areas or laboratory for conformance with established sampling and testing protocols, analytical methods, and specifications. For example, evaluate the tests for weight variation, hardness, and friability. These tests may be performed every fifteen or thirty minutes during tableting or encapsulating procedures. All testing must comply with CGMP's.

The drug application may contain some of the in-process testing plan, including methods and specifications. The inspection must confirm that the in-process tests were done, as described in the plan, and ascertain that the results were within specifications. The laboratory work for the lengthier tests should also be reviewed.

The methods used for in-process testing may differ from those used for release testings. Usually, whether the methods are the same or different, the specifications may be tighter for the in-process

tests. A product with a 90.0%-110.0% assay release specification may have a limit of 95.%-105.0% for the in-process blend. Some of the tests done may differ from those done at release. For example, a firm may perform disintegration testing as an in-process test but dissolution testing as a release test.

Expect to see consistent in-process test results within batches and between batches of the same formulation/process (including development or exhibit batches). If this is not the case, expect to see scientific data to justify the variation.

19. STABILITY

A stability-indicating method must be used to test the samples of the batch. If there is no stability-indicating assay additional assay procedures such as TLC should be used to supplement the general assay method. Evidence that the method is stability indicating must be presented, even for compendial methods. Manufacturers may be required to accelerate or force degradation of a product to demonstrate that the test is stability indicating. In some cases the sponsor of ANDA's may be able to search the literature and find background data for the specificity of a particular method. This information may also be obtained from the supplier of the drug substance. Validation would then be relatively straightforward, with the typical parameters listed in the USP in chapter <1225> on validation of compendial methods addressed as applicable.

Evaluate the manufacturer's validation report for their stability testing. Again, review the raw laboratory data and the results of testing at the various stations to determine if the data actually reported matches the data found in on site records.

Evaluate the raw data used to generate the data filed documenting that the method is stability indicating and the level of impurities.

20. COMPUTERIZED LABORATORY DATA ACQUISITION SYSTEMS

The use of computerized laboratory data acquisition systems is not new and is addressed in the following CGMP guidance documents:

- Compliance Policy Guide 7132a.07 Computerized Drug Processing: Input/Output Checking.
- Compliance Policy Guide 7132a.08 Computerized Drug Processing: Identification of "Persons" on Batch Production and Control Records.
- Compliance Policy Guide 7132a.11 Computerized Drug Processing: CGMP Applicability to Hardware and Software
- Compliance Policy Guide 7132a.12 Computerized Drug Processing: Vendor Responsibility

- Compliance Policy Guide 7132a.15 Computerized Drug Processing: Source Code for Process Control Application Programs
- Guide to Inspection of Computerized Systems in Drug Processing.

It is important, for computerized and non computerized systems, to define the universe of data that will be collected, the procedures to collect it, and the means to verify its accuracy. Equally important are the procedure to audit data and programs and the process for correcting errors. Several issues must be addressed when evaluating computerized laboratory systems. These include data collection, processing, data integrity, and security.

Procedures should only be judged adequate when data are secure, raw data are not accidentally lost, and data cannot be tampered with. The system must assure that raw data are stored and actually processed.

The agency has provided some basic guidance on security and authenticity issues for computerized systems:

- Provision must be made so that only authorized individuals can make data entries.
- Data entries may not be deleted. Changes must be made in the form of amendments.
- The data base must be made as tamperproof as possible.
- The Standard Operating Procedures must describe the procedures for ensuring the validity of the data.

One basic aspect of validation of laboratory computerized data acquisition requires a comparison of data from the specific instrument with that same data electronically transmitted through the system and emanating on a printer. Periodic data comparisons would be sufficient only when such comparisons have been made over a sufficient period of time to assure that the computerized system produces consistent and valid results.

21. LABORATORY MANAGEMENT

Overall management of the laboratory work, its staff, and the evaluation of the results of analysis are important elements in the evaluation of a control laboratory. Span of supervisory control, personnel qualifications, turnover of analysts, and scope of the laboratory's responsibility are important issues to examine when determining the quality of overall management and supervision of work. Individually or collectively, these factors are the basis for an objection only when they are shown to result in inadequate performance of responsibilities required by the CGMPs.

Review laboratory logs for the sequence of analysis and the sequence of manufacturing dates. Examine laboratory records and logs for vital information about the technical competence of the staff and the quality control procedures used in the laboratory.

Observe analysts performing the operations described in the application. There is no substitute for actually seeing the work performed and noting whether good technique is used. You should not stand over the analysts, but watch from a distance and evaluate their actions.

Sometimes the company's employees have insufficient training or time to recognize situations that require further investigation and explanation. Instead they accept unexplained peaks in chromatograms with no effort to identify them. They may accept stability test results showing an apparent increase in the assay of the drug with the passage of time with no apparent question about the result. Also, diminishing reproducibility in HPLC chromatograms appearing several hours after system suitability is established is accepted without question.

Good manufacturing practice regulations require an active training program and the documented evaluation of the training of analysts.

The authority to delete files and override computer systems should be thoroughly examined. Evaluate the history of changes to programs used for calculations. Certain changes may require management to re-examine the data for products already released.