Gerhard Nahler

Dictionary of Pharmaceutical Medicine

Third Edition

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With contribution by Annette Mollet

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Gerhard Nahler
Clinical Investigation Support
Pharmaforschung GmbH
Wien
Austria

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Foreword

In the beginning was the word – and the foreword. Words are combined to sentences and eventually language. Words are listed in a dictionary and their meaning in building language are explained in a lexicon. In the life sciences – e.g. drug development sciences and pharmaceutical medicine – the analogies are evidenced by the genomic library and patho-physiological function as the lexicon. In this transition from code to function integrated lexica pay a pivotal role for a faster understanding. The present updated version of this books combines dictionary and lexicon and provides the translational understanding of the complex drug development process. With a large number of new terms, their abbreviations and explanations in this complex interdisciplinary process a great number of different disciplines and specialists need to be informed: they include physicians, pharmacists, biologists, chemists, biostatisticians, data managers, information specialists, business developers, marketing experts as well as regulators, financing specialists, healthcare providers and insurers in a continuous professional development mode. This lexicon is therefore a most suitable and economical tool for fast and conclusive information for all key-players in the development of medicines at the working place, in postgraduate training as well as during graduate education. This book is an indispensible aid in any medical library.

Prof. Dr. med. Dr. h.c. Fritz R. Bühler
Director, European Center of Pharmaceutical Medicine
ECPM at the Medical Faculty and the PharmaCenter
University of Basel Co-ordinator
Pharmaceutical Medicine Training
Programme of the Innovative Medicines Initiative
IMI, Joint Undertaking of EC and EFPIA

Preface

Over the last few years pharmaceutical medicine has evolved with a speed never seen before. Pharmaceutical medicine comprises clinical pharmacology, molecular biology, pharmacotherapy, toxicology, pharmacovigilance, epidemiology, chemistry, drug manufacturing, regulatory and legal affairs, marketing, statistics, data management, and a number of additional areas such as health care and insurance. Even alimentation is important for the effects of medications if one considers the possibility of interactions as an example. The ongoing evolution of above mentioned areas has resulted in a rapid increase of new guidelines issued by health authorities as well as in adaptations of those that already exist. As an example, the European Community Directive 2001/83/EC, relating to medicinal products for human use, has been amended nine times between 2001 and 2011, by Dir 2002/98, Dir 2003/63, 2004/24, 2004/27, Dir 2008/29, 2009/53, 2009/120, 2010/84, 2011/62. Efforts were made in this book to scope with these changes. I beg for the user's indulgence if anything has been omitted that would have been useful in the eyes of the user. It is absolutely necessary that the user familiarises him- or her with the original, most actual texts for further information.

This ongoing evolution has also led in some cases to a slight change in our understanding and common use of terms, e.g. "study" versus "trial", both of which are often used synonymously, but also to the creation of new terms and their abbreviations with the result that some might be faced with a Babylonian disarray of language. More than once one person may interpret and understand the same term in a different way from another. Hopefully this book contributes in reducing such ambiguities. Where "true" synonyms exist such as e.g., "monitor's visit log list / site visit log / monitoring log list / appointment log" they are included in the text in order to make clear that these terms mean the same.

This dictionary gives short explanations to about 2,000 terms, in addition to over 600 commonly used acronyms. The book is not an exhaustive presentation of all areas of pharmaceutical medicine but intends to be a "first aide" in the

understanding of these terms on one hand as well as in their context on the other. For that, such relationships are highlighted by cross-references in small capitals. Where it might be useful, links to websites of institutions are included. Finally, important documents and science oriented websites are listed in the back matter of this book where the user can find further information. This part includes also a directory of important national and international bodies, authorities and societies with their websites. This will facilitate to establish contacts and to get further help.

Gerhard Nahler

Contents

Dictionary of Pharmaceutical Medicine

A

abbreviated new drug application (ANDA) Application for MARKETING AUTHORISATION if a drug has already received approval under a previous conventional NDA; important drug properties as e.g. toxicity and safety have therefore already been documented; see also ABRIGED APPLICATION, ACCELERATED APPROVAL PROGRAM, APPROVAL.

Aberdeen drug coding system see CODE.

abriged application EC: "the applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate: (i) either that the PROPRIETARY MEDICINAL PRODUCT is essentially similar to a product authorized … and that the person responsible for the marketing of the original product has consented to the … references contained in the file being used … (ii) or by detailed references to published scientific literature … (iii) or that the product is ESSENTIALLY SIMILAR to a product which has been authorized within the Community … for not less than 6 (10) years and is marketed in the Member State for which the application is made … ; … where the … product is intended for a different therapeutic use from that of the other products marketed or is to be administered by different routes or doses, the results of appropriate pharmacological and toxicological tests and/or clinical trials must be provided"; see also ABBREVIATED NEW DRUG APPLICATION, ACCELERATED APPROVAL PROGRAM, BIBLIOGRAPHICAL APPLICATION, GENERIC APPLICATION, HYBRID PROCEDURE.

absolute bioavailability see BIOAVAILABILITY.

absolute risk see RISK.

absorption Process by which a drug enters the body; enteral absorption is most readily with non-ionized lipid-soluble drugs (e.g. ethanol), weak acids with pKa >3 and weak bases with pKa <7.8 are also very well absorbed;

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absorption in the stomach becomes critical, if the drug has a very low solubility in water (<5 mg/ml) or a low lipid/water partition coefficient, or if the disintegration-/dissolution time is low; see ADME, ADMINISTRATION, BIOAVAILABILITY, DISINTEGRATION TEST, FIRST PASS EFFECT, pKa, ROUTE OF ADMINISTRATION.

abstinence syndrome see DEPENDENCY, WITHDRAWAL (SUBSTANCE).

academic study see NON-COMMERCIAL CLINICAL TRIAL.

accelerated approval program syn. fast track procedure; approval of therapies with an "added benefit" i.e. "that provide a meaningful therapeutic benefit for patients with serious illness" (FDA) will be accelerated; a similar procedure exist in the EC; in this case, approval relies solely or in part on surrogate endpoints for evidence of effectiveness; the average duration for marketing authorisation in the US takes more than 20 months; in an accelerated approval program substances are classified according to their therapeutic potential in P (priority) and S (standard) substances; see ABBREVIATED NEW DRUG APPLICATION, ADVANCED THERAPY, APPROVAL, NEW DRUG APPLICATION, SURROGATE ENDPOINT, THERAPEUTIC POTENTIAL.

accelerated testing see STRESS TESTING.

acceptable daily intake (ADI) Maximal amount of trace element, mineral and other substances which can be taken lifelong without any harm to HEALTH; see also ALIMENTARY RISKS, BIOBURDEN, DEFINED DAILY DOSE.

acceptable quality level (AQL) defined as the maximum percent of errors that, for purposes of controls or sampling, can be considered satisfactory as an average of the total system or process; see also AUDIT.

accrual rate see RECRUITMENT RATE.

accuracy Extent to which a measurement agrees with the "true" value (which is never known) of the analyte being assayed; a. reflects the extent of a systematic ERROR; the result obtained with the method in question is usually compared with values obtained by an acceptable reference method; (validation); results may be accurate, i.e. lying within acceptable boundaries, but still imprecise, because they are widely scattered; see CONFIDENCE INTERVAL, MEASUREMENT PROPERTIES, PRECISION.

acid dissociation constant see pKa.

acknowledgements Authors of publications frequently use a. to thank persons who made technical or intellectual contributions ("contributors") to a study which were not deemed sufficient to qualify for AUTHORSHIP; it may be questionable if a. should also include people who simply did their routine jobs

without any special contributions; (http://www.icmje.org/ethical_1author.html). See also AUTHORSHIP, PUBLICATION GUIDELINES.

action letter Official letter of the FDA to a sponsor company, informing e.g. on an NDA decision by the agency; two types exist: since mid of 2009 (i) an approval letter which allows marketing of the product, (ii) a not approvable letter (complete response letter) which describes important deficiencies that preclude approval unless corrected; a new review cycle may be started after resubmission of an application; see also NEW DRUG APPLICATION.

active implantable medical device see MEDICAL DEVICE.

active (pharmaceutical) ingredient (API) syn. active substance, drug substance; pharmacologically active part(s) of a FORMULATION; in case of a salt, the active ingredient should be understood to include both, the therapeutic moiety and the appended portion of the molecule; the maximum acceptable deviation in the a.i. content of a finished product must not exceed ±5 % at the time of manufacture; it is estimated that about 10,000 different APIs exist; see also ADDITIVE, DOSAGE, DRUG, FORM, FORMULATION, MEDICINAL PRODUCT, RETEST PERIOD, STABILITY.

active medical device see ACCELERATED APPROVAL PROGRAM MEDICAL DEVICE.

active site The part of a protein that must be maintained in a specific shape if the protein is to be functional, for example, the part to which the substrate binds in an enzyme or, resp., the part of an enzyme where the actual enzymatic function is performed.

active substance syn. drug substance; see DRUG, MEDICINAL PRODUCT; often used synonymously to ACTIVE PHARMACEUTICAL INGREDIENT.

active substance master file see DRUG MASTER FILE.

active substance starting material Raw material, intermediate, or an active substance that is used in the production of an active substance; see also ACTIVE INGREDIENT, DRUG, MEDICINAL PRODUCT.

activities of daily living (ADL) Include typically the following activities: sitting, putting on socks and shoes, getting in/out of a chair/car, standing, walking; in general, these activities are scored using an ORDINAL SCALE, ranging from e.g. "0", no impairment, to "4", total inability to perform the activity.

actual marketing see PLACING ON THE MARKET, see also SUNSET CLAUSE.

actual-treated analysis syn. as-treated analysis; opposite to intent-to-treat a.; see INTENT-TO-TREAT ANALYSIS, PER-PROTOCOL ANALYSIS, VALID CASE ANALYSIS.

A

actuarial method see SURVIVAL ANALYSIS.

acute toxicity Single or multiple exposures in a short space of time, usually less than 24 h; see TOXICITY.

adaptation In the evolutionary sense, some heritable feature of an individual's phenotype that improves its chances of survival and reproduction in the existing environment.

adaptive design syn. flexible design; clinical trial design where trial and/or statistical procedures are modified after the initiation according a prospective plan in an ongoing way, based on accrued data; however, many a.d. are not suitable for trials with a long treatment duration/where adaption depends on response of previous subject; furthermore, quality, integrity and validity of the trial may be at a greater risk as there are many sources of BIAS; commonly considered adaptive designs are: adaptive randomization d., response adaptive d. (at each patient visit, the investigator decides whether to switch a patient's treatment depending on the patient's outcome to date), group sequential d., sample-size re-estimation d., drop-the loser (or pick-the winner) d., adaptive dose finding d., biomarker adaptive d., adaptive treatment-switching d., adaptive-hypothesis d., adaptive seamless trial d., multiple adaptive d., a.o.; see also DESIGN.

added benefit see ACCELERATED APPROVAL PROGRAM COST/BENEFIT ANALYSIS.

addendum Usually a "minor" change to a PROTOCOL of a CLINICAL TRIAL (without consequences on ethical aspects); see also AMENDMENT.

additives Substances (ingredients) added to ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) to improve the final formulation; see ADJUVANT, ANTIOXIDANTS, DISINTEGRANTS, EXCIPIENTS, FORMULATION, PRESERVATIVES.

additive effect see INTERACTION OF DRUGS; see also EFFECT MODIFIERS, ERROR.

additional monitoring Pro-active surveillance of efficacy and safety of a medicinal product; EC Regulation 1235/2010 states that EMA maintains a "public list of products that are subject of additional monitoring"; this includes products that contain a new active substance or a biological product that was not authorized in the EC on 01 January 2011 (they may be removed from the list after 5 years), but also products where "observations raise important new questions of a scientific or technical nature"; in such cases, the respective SPC must include a black symbol and the statement: "This medicinal product is subject to additional monitoring"; see also BLACK BOX WARNING, BLACK TRIANGLE, INTENSIVE MONITORING, PHARMACOVIGILANCE, POST-AUTHORISATION STUDY, PRESCRIPTION-EVENT MONITORING, SOLICITED REPORTS.

adjuvant Pharmacological or immunological agent that modifies the effect of other agents such as a DRUG or VACCINE; see also DISINTEGRANT, EFFECT MODIFIERS.

Adjuvant chemotherapy Systemic chemotherapy administered after the use of definitive loco-regional treatment (resection of all known tumour); histological assessment of the resected tumour specimen allows allocation of a pathological stage, thus predication of likely outcome without further intervention; see also NEOADJUVANT CHEMOTHERAPY.

ADME abbr. ABSORPTION, DISTRIBUTION, METABOLISM, and/or ELIMINATION of a drug as a guide to the DESIGN of early CLINICAL TRIALS in PHASE I and definitive PHARMACOKINETIC studies.

administration of a substance can be enteral (directly into the gastrointestinal tract), i.e. oral, rectal, sublingual, nasal or parenteral (bypassing the gastrointestinal tract), i.e. intravenous, intramuscular, subcutaneous, intra-arterial, intraperitoneal etc.; see ABSORPTION, ADME, ROUTE OF ADMINISTRATION.

admission criteria see ELIGIBILITY CRITERIA.

adolescent see AGE GROUPS.

advanced therapy EC: "advanced therapy medicinal product" (ATMP) are industrially manufactured products that are based on genes (GENE THERAPY), somatic cells (cell therapy, e.g. stem cells) or tissues (tissue engineered product that contains or consists of engineered cells or tissues); they can also be combinations of and are used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue; this excludes products acting primarily by physical means (Reg 1394/2007; Dir 2009/120; Reg 726/2004); see also ACCELERATED APPROVAL, COMMITTEE OF ADVANCED THERAPIES (CAT), PERSONALISED MEDICINE, STEM CELL THERAPY.

adverse drug event (ADE) see ADVERSE REACTION, CONCOMITANT EVENT, DRUG-EVENT COMBINATION, DRUG INJURY, PHARMACOVIGILANCE, RULE-OF-THREE.

adverse drug experience (ADE) Can either be expected (labelled) which means that the event is listed in the current (FDA-) approved labelling for the drug as a possible complication of drug use or unexpected (unlabeled), the latter term includes an event that may differ from a labelled reaction because of greater severity or specificity (e.g. abnormal liver function vs. hepatic necrosis); reports of death from an ADE are considered unlabeled unless the possibility of a fatal outcome from that ADE is stated in the labelling; see also ADVERSE DRUG EVENT, LABELING.

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adverse drug reaction (ADR) ICH: (pre-approval clinical experience): "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reaction"; WHO/ICH (marketed medicinal product): "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function"; CIOMS (COUNCIL FOR INTERNATIONAL ORGANISATION OF MEDICAL SCIENCE) reports always refer to a suspect reaction (in contrast to event or experience), which implies that a physician or other professional health care worker has judged it a reasonable possibility that an observed clinical occurrence has been caused by a drug; some authorities (e.g. Japan) recommend to document a sufficient number of subjects to detect ADRs with an incidence of 0.1 %; in the SUMMARY OF PRODUCT CHARACTERISTICS (SPC) the term "UNDESIRABLE EFFECTS" is used; see also ADVERSE REACTION, DRUG INJURY, EXPEDITED REPORTING, IMMUNOLOGIC REACTION, SPONTANEOUS ADVERSE DRUG REACTION REPORT, TREATMENT EMERGENT SIGNS AND SYMPTOMS, (UN)LISTED ADVERSE DRUG REACTION.

adverse event (AE) ICH: "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment"; any undesirable experience occurring to a subject during a clinical treatment, whether or not considered related to the (investigational) product(s); expected AE = event which is already known from previous experiences and described in the INVESTIGATOR'S BROCHURE or package insert; techniques to evaluate AEs are e.g.: CASE CONTROL STUDIES, POST-MARKETING SURVEILLANCE programmes, PRESCRIPTION-EVENT MONITORING, PRESCRIPTION-SEQUENCE ANALYSES etc.; when an AE has been assessed (see STANDARDISED ASSESSMENT OF CAUSALITY) and there are reasonable grounds for the suspicion that it is causally related to the (investigational) drug(s), it must be considered as an ADVERSE DRUG REACTION; for regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an ADR; see also ADVERSE EXPERIENCE, ADVERSE REACTION, BLINDING, CONCOMITANT EVENT, INCIDENT, MEDICAL DEVICE REPORTING, PHARMACOVIGILANCE, RULE OF THREE, SAFETY UPDATE REPORT, SIGNIFICANT ADVERSE EVENT, UNEXPECTED ADVERSE EVENT.

adverse event of special interest AE (serious or non-serious) of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate (ICH E2F, CIOMS VII); suspected unexpected serious adverse reactions (SUSARs) are always of special interest; see ADVERSE EVENT, PATIENT SUPPORT PROGRAM.

adverse event report format see CIOMS FORM, EMA, FDA.

adverse event reporting system (AERS) National database for adverse events of the FDA (VAERS for vaccine adverse events reporting system); see PHARMACOVIGILANCE, SIGNAL, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING SYSTEM.

adverse experience (AE) Term used mainly in US; considered interchangeable with ADVERSE EVENT.

adverse reaction (ADR) Reaction which is suspected to be causally related to the intake of a pharmaceutical product "which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [Dir 2001/83, Art.1(11)]; this has been amended (Dir 2010/84/EU) to: "noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product"; (ARs associated with a medication error, misuse or abuse have been included); intensity rating scale: mild = awareness of a sign or symptom which is easily tolerated and reversible, moderate = reversible, but discomfort is enough to cause interference with usual activity, severe = incapacitating with inability to work or undertake usual activity; seriousness: ICH: "a serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose (i) results in death, (ii) is life-threatening (i.e. an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), (iii) requires inpatient hospitalisation or prolongation of existing hospitalisation, (iv) results in persistent or significant disability/incapacity, (v) is a congenital anomaly/birth defect, or is an other medically important condition" (e.g. increase in the rate of occurrence of an expected sAE, significant hazard such as lack of efficacy, major safety finding from a new animal study); FDA: serious = ADR which is "LIFE-THREATENING, requires inpatient hospitalization, prolongs hospitalization, permanently or severely disabling, or requires prescription drug therapy: the following types are always considered serious: death, congenital anomaly, cancer, or overdose"; serious (EC) = ADR which is "fatal, LIFE-THREATENING, disabling, incapacitating, or which results in or prolongs hospitalisation or is a congenital anomaly/birth defect"; classification of reaction: type A = "augmented", reactions of a predictable nature, following a known response pattern; type B = "bizarre", effects that are unpredictable (hypersensitivity or IDIOSYNCRATIC REACTIONS); type C = "chronic", effects that occur with long term use of a drug (cataract with corticosteroids); type D = "delayed", effects that occur remote from use (vaginal cancer in female

offsprings of women who took diethylstilbestrol during pregnancy); type E = "exit", rare reactions after stopping a medication (e.g., myocardial ischemia after sudden stop of ß-blockers); type F = "failure", a treatment effect that can reasonably be expected is not observed, e.g., no antibodies formed after vaccination; timing (ICH): "acute" <1 h, sub-acute < 1 day, latent > 1 day; EC regulations foresee reporting of (spontaneous) serious ADRs (labelled or unlabelled/unexpected) to the competent authority as soon as possible but not later than 7 calendar days after first knowledge by the sponsor (for which the CIOMS-FORM is recognised by a number of EC-member states; other regulatory report forms are the FDA 1639 (US) and the YELLOW CARD in UK), followed by a written report as complete as possible within 8 additional calendar days (FDA: 15 working days, "fifteen days report"), including assessment of causality; a second type of report are PERIODIC SAFETY UPDATE REPORTS (EC: half-yearly for the first 2 years of marketing and annually thereafter for the first 5 years, than every 3rd year; FDA: quarterly for the first 3 years and annually thereafter); outcome: unchanged; recovered = patient returned to his previous health status with no subsequent problems; not yet recovered = patient has not yet returned to his previous health status and continues to be followed for the adverse event, but is expected to recover without sequelae; sequelae = patient has a permanent change in health status subsequent to the ADR; fatal = patient died (indication of date, cause, if an autopsy was performed and autopsy report); unknown = outcome of event unknown; unexpected (unlabelled, unknown) ADR or Suspected Unexpected Serious Adverse Reaction (SUSAR) = a reaction that is "not listed in the current labelling for the drug (EC: SPC) as having been reported or associated with the use of the drug" (FDA); ICH: "an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational medicinal product)"; this includes an ADR that may be symptomatically or patho-physiologically related to a known ADR, but differing in nature, severity or incidence (frequency) with regard to information given in the current labelling (REFERENCE SAFETY INFORMATION), e.g. PACKAGE INSERT, INVESTIGATOR'S BROCHURE, in the general INVESTIGATOR'S PLAN, or elsewhere; serious ADRs and SUSARs are to be reported with 15 days (death within 7 days + 8 days for follow-ups), non-serious ADRs within 90 days at the latest to the EudraVigilance database of the EC; the clinical trial protocol or IB can identify those serious ARs that do not require immediate reporting (Guidance 2011/C 172/01, e.g., those that are included in the reference safety information); methods for assessments are e.g. spontaneous (voluntary) reporting, intensive (hospital-based) drug surveillance, record linkage or case–control studies; incidence (ICH): very common: >10 %, common: 1–10 %, uncommon: 0.1–1 %, rare: 0.01–0.1 %, very rare: <0.01 %; it has been estimated that in 2011 about 2.4–5.8 % of the hospitalizations in

Germany were caused by ARs and that 197,000 deaths are caused by ARs annually in the EU (Commission of the European Community 10 Dec 2008, Summary of the Impact Assessment SEC(2008) 2671); see also ADVERSE EVENT, BLACK TRIANGLE, CAUSALITY, CONSUMER REPORT, CORE DATA SHEET, CRITICAL TERM LIST, DRUG ABUSE, DRUG-EVENT COMBINATION, DRUG INJURY, EXPEDITED REPORTING, INCIDENCE, INDIVIDUAL CASE SAFETY REPORT, INTENSIVE MONITORING, MISUSE, PARENT–CHILD/FOETUS REPORT, PERIODIC SAFETY UPDATE REPORT, S-2 REPORT, SIGNIFICANT OVERDOSE, WHO-ADVERSE REACTION TERMINOLOGY, WHO COLLABORATING CENTER FOR INTERNATIONAL DRUG MONITORING, WHO-DRUG REFERENCE LIST.

adverse reaction databases see WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING.

age see GERIATRIC POPULATION.

age groups Age groups may be defined as follows (ICH, EMA): preterm newborn infants (<36 weeks gestation), term newborn infants (0–28 days), infants and toddlers (28 days – 23 months), children (2–11 years), adolescents (12–18 years), adults (18–65 years), elderly (>65 years); for INDIVIDUAL CASE SAFETY REPORTS age groups are "foetus, neonate, infant, child, adolescent, adult, elderly"; [ICH E2B(R3)]; see also ELDERLY, GERIATRIC EVALUATIONS, PEDIATRIC POPULATION, VULNERABLE SUBJECT.

Agency (EMA) former: European Medicines Evaluation Agency (EMEA); see EUROPEAN MEDICINES AGENCY.

Agency for Toxic Substances & Disease Registry (ATSDR) Federal public health agency of the U.S. Department of Health and Human Services; provides health information to prevent harmful exposures and diseases related to toxic substances. http://www.atsdr.cdc.gov/; see also ENVIRONMENTAL RISK ASSESSMENT.

age-specific rate def.: rate of an outcome calculated for a certain age group; only individuals in the designated age range are included in the numerator and denominator; see also INCIDENCE, OUTCOME MEASUREMENT, PREVALENCE RATE.

air-lock EC (IV): "An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered; an a.-l. is designed for and used by either people or goods."

AJCC Staging (= American Joint Committee of Cancer) see TNM.

A

ALCOA see DATA QUALITY.

alert report see EXPEDITED REPORT.

algorithm Procedure permitting various choices among alternative decisions to reach a result.

alimentary risks A number of substances are found, particularly in industrial food, that have been linked to potential serious health problems: TRANS FATS (components of many industrial foods) have been estimated in 1994 to have caused 20,000 deaths annually in the US from heart diseases but are also linked to diabetes and cancer; acrylamide in food such as bread or other baked products may induce diabetes and cancer, or bisphenol A in plastic containers that can damage the developing brain or induce erectile dysfunction; PESTICIDES on dried teas, fruits such as apples or vegetables such as tomatoes have also been linked to fertility disorders, diabetes and cancer as many of such pesticides have hormonal effects; other risks arise from microorganisms and from contaminations such as with viruses or PRIONS, that cause about 300 deaths annually in the US or from chemicals such as methylmercury released to seawater and concentrated along the food chain (fish) causing 1968 the "Minamata disease" in Japan; other sources of a.r. are mycotoxins (e.g., aflatoxins in peanuts) or cadmium (dyes, fertilizers); risks are not limited to food only; e.g. drinking water may contain byproducts that result from disinfection with chlorine, ozone, chlorine dioxide or chloramines such as modified organic compounds that may be cancerogenic (e.g. bromate, chlorite, haloacetic acids); see also AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY (ATSDR), ALLOWED DAILY DOSE, BIOACTIVE COMPOUNDS, CYTOCHROMS P450 (CYP P450), ENVIRONMENTAL RISK ASSESSMENT, GENETIC ENGINEERING, NANOPARTICLES, THRESHOLD OF TOXICOLOGICAL CONCERN, TOTAL ORGAN CARBON, http://www.pan-europe.info/index.php.

allele Any of several alternative forms of a given GENE at a specific locus; see also CYTOCHROMES P450, DOMINANT, GENETIC VARIANCE, GENOME, HETEROCYGOUS, HOMOCYGOUS, POLYMORPHISM, RECESSIVE, SINGLE NUCLEOTIDE POLYMORPHISM.

allele frequency Often called gene frequency; a measure of how common an allele is in a population; the proportion of all alleles at one gene locus that are of one specific type in a population.

allelic exclusion A process whereby only one immunoglobulin light chain and one heavy chain gene are transcribed in any one cell; the other genes are repressed.

allergen product EC (I): "any product which is intended to identify or to induce a specific acquired alteration in the immunological response to an allergizing agent"; see also BIOLOGICAL MEDICINAL PRODUCT.

allocation see RANDOMISATION.

allogenic Of the same species, but with a different genotype.

allopathy Def. (WHO) "Non-traditional, western scientific therapy, usually using synthesised ingredients, but may also contain a purified active ingredient extracted from a plant or other natural source; usually in opposition to the disease"; see also ALLOPATHY, ALTERNATIVE MEDICINE, HOMEOPATHY.

allosteric regulation Regulation of an enzyme's activity by binding of a small molecule at a site that does not overlap the ACTIVE SITE region.

allotype The protein product (or the result of its activity) of an allele which may be detected as an antigen in another member of the same species (e.g. histocompatibility antigens, immunoglobulins), obeying the rules of simple Mendelian inheritance.

allowed daily dose Human exposure threshold value for chemicals above which an increasing risk to human health is assumed; see also ACCEPTABLE DAILY INTAKE, DEFINED DAILY DOSE, MAXIMUM RESIDUE LIMIT, RECOMMENDED DAILY/DIETARY ALLOWANCES, THRESHOLD OF TOXICOLOGICAL CONCERN.

alpha error syn. type I error; statistical risk of saying there is a difference between treatments when there is none ("false alarm"; truth: $A = B$, false judgment: $A > \text{or} < B$); usually called P-VALUE with $p < 0.05$; error of falsely rejecting a NULL HYPOTHESIS; see also BETA ERROR, BONFERRONI CORRECTION, GAMMA ERROR, INTERIM ANALYSIS.

alternative hypothesis (Ha) Postulate of a clinically important (treatment-) difference or degree of association between two groups; see also BETA ERROR, DELTA VALUE, NULL HYPOTHESIS.

alternative medicine syn. non-conventional or traditional or natural medicine; health care practices that are not integrated into the dominant health care system and usually not covered by health insurance; most treatments have not been objectively tested according to accepted standards of conventional medicine; see also APITHERAPY, BALNEOTHERAPY, COMPLEMENTARY MEDICINE, FUNCTIONAL FOOD, INTEGRATIVE MEDICINE, ORTHOMOLECULAR MEDICINE, PHYTOMEDICINES; see also ALLOPATHY, HOMEOPATHY.

alternative splicing Various ways of splicing out introns in eukaryotic pre-mRNAs resulting in one gene producing several different mRNAs and protein products.

amendment Term often used for "major" change(s) to a PROTOCOL relating to ethical aspects as e.g. a new risk/benefit relation by an increase in treatment

duration or doses and needing therefore resubmission and approval by an ETHICS COMMITTEE in contrast to an ADDENDUM (= minor change without consequences on ethical aspects); there may be reasons for urgent amendments in clinical trials such as QT-prolongation, unexpected liver toxicity that need immediate contacting of the health authority.

Ames test Widely used test to detect possible chemical carcinogens; based on mutagenicity in the bacterium Salmonella typhimurium; see also in vitro MUTAGENICITY TEST, TOXICITY TESTING.

amino acids Molecules that build up peptides and proteins; there are 20 common (essential) amino acids: alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine; they exists as d- and l- ENANTIOMERS. An example for a non-protein-forming a.a. with clinical relevance is homocysteine, a risk factor/marker for cardiovascular diseases and dementia; see also BIOMARKER, CHIRALITY, PROGNOSTIC/PREDICTIVE MARKER.

analysis see BIOANALYTICAL METHOD, ECOLOGICAL FALLACY, EFFECT SIZE, ERROR, EXPLANATORY TRIAL, EXTENDER A., INTENT-TO-TREAT A., PER-PROTOCOL A, STANDARDIZED RESPONSE MEAN.

analysis certificate see RELEASE CERTIFICATE.

analysis of study results Analysis of study results may be done in different ways, whether all patients are considered or not; the INTENT-TO-TREAT A. (1) considers statistical analysis of DATA from all randomized patients, whether they were in full compliance with the study PROTOCOL or not, that is without omitting defaulters; the last values available from all patients are pooled for analysis (Last Visit Carried Forward – technique); although this procedure is artificial, results are less likely to be disturbed by DROP-OUTS especially if they are similar frequent in the groups to be compared; in contrast, the AS-TREATED A. (2) considers drop-outs, missed doses, erroneous doses, wrong diagnosis a.s.o.; all data of all patients are included as they are available (evaluable); analysis of subjects "as eligible" (3) excludes patients violating the selection criteria; other possibilities of analyses are: (4) a. of "completers" only, where there is a risk that results are distorted by drop outs, and a. "PER PROTOCOL" (5) which excludes major protocol violators; (6): sometimes it may be justified to exclude those patients who dropped-out during a run-in period ("all subjects dosed" a.), usually at least two types of analyses are provided for randomized CLINICAL TRIALS: ITT-analysis and an additional a. of one of the types mentioned which should give comparable results; all a. excluding patients are more likely to be subject to BIAS due to selection mechanisms which may antagonize

RANDOMISATION; see also COMPLETE CASE A, ERROR, LAST VALUE CARRIED FORWARD, VALID CASE A.

anatomical therapeutic chemical classification system (ATC) Recommended by the WHO for use in drug utilization studies (http://www.whocc.no/atc_ddd_index/); drugs are divided into different groups and codified according to their main site of action as well as therapeutic and chemical characteristics; the first 1-digit represents the anatomo-physiological class, the second 2-digits represent the pharmacological class, the third 1-digit represents the pharmacological sub-class, the last 1-digit represents the therapeutic class; ATC-codes may be updated; useful also as basis for setting up therapeutic groups for REIMBURSEMENT; see also DEFINED DAILY DOSE (DDD), WHO-DRUG REFERENCE LIST.

anchored visual analogue scale syn. "categorized" VAS; see LIKERT SCALE, VISUAL ANALOGUE CALE.

anecdotal study see OBSERVATIONAL STUDY.

aneugen Substance causing toxic effects upon genetic material (DNA) of cells, inducing permanent and transmissible genomic mutations (numerical aberrations with changes – gain or loss – of chromosomes); see also CLASTOGEN, GENOTOXICITY, TOXICITY TESTS.

animal pharmacology Before the first application of new drugs in men they usually undergo extensive testing in various animal species; see also PHARMACOLOGY.

ankle-brachial index (ABI) ratio of the systolic blood pressure in the a. dorsalis pedis or posterior tibial artery in the leg divided by the systolic pressure in the brachial artery of the arm; commonly used parameter for assessing Peripheral Artery Disease (PAD).

annual progress report Report required by ETHICS COMMITTEES to inform them on the status and progress of a particular CLINICAL TRIAL; this report is not identical to the ANNUAL SAFETY UPDATE REPORT; a.p.r. can be milestones in RISK MANAGEMENT; see also INVESTIGATOR'S BROCHURE.

annual safety report (ASR) has been replaced in the EC by the DEVELOPMENT SAFETY UPDATE REPORT (DSUR).

annual safety update report (ASUR) Report to provide health authorities and ETHICS COMMITTEES with new safety information and an updated risk/benefit evaluation pertinent to the CLINICAL TRIAL program (one or more clinical trials) with a particular product; this report is not identical to the DSUR although some safety information overlaps; as of 01 September 2011 only DSUR

submissions will be accepted in the EU; the ASUR overlaps also with the safety information in the INVESTIGATOR'S BROCHURE; see ANNUAL PROGRESS REPORT, DEVELOPMENT SAFETY UPDATE REPORT (DSUR), SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION/SUSAR.

anonymised see CODE.

antagonism see INTERACTION OF DRUGS.

anthropometry Measurements include e.g., the BODY MASS INDEX, skin-fold measurement, upper mid-arm circumference, WAIST-HEIGHT-RATIO, WAIST-HIP RATIO, WAIST CIRCUMFERENCE etc.; see also BODY COMPOSITION, LORENTZ FORMULA, MOSTELLER FORMULA.

antibiotic Chemical substance formed as a metabolic by-product in bacteria or fungi and used to treat bacterial infections; antibiotics can be produced naturally by fermentation, using microorganisms, or synthetically.

antibody A protein produced by the immune system in response to an antigen (a molecule that is perceived to be foreign); antibodies bind specifically to their target antigen to help the immune system destroy the foreign entity.

anticodon Triplet of nucleotide cases (codon) in transfer RNA that pairs with (is complementary to) a triplet in messenger RNA; for example, if the codon is UCG, the anticodon might be AGC.

antigen A substance to which an antibody will bind specifically.

antioxidant Substances (e.g. ascorbic acid, sulphites, ascorbyl palmitate, alkyl gallate, hydrochinone, tocopherols) used in pharmaceutical FORMULATIONS to inhibit the reaction with oxygen in the surrounding atmosphere; they can react with free radicals to form stable or meta-stable products, thus terminating the oxidation reaction; see BIOACTIVE COMPOUNDS, EXCIPIENTS, DISINTEGRANTS, FORMULATION, PRESERVATIVES.

antisense drug see ANTISENSE OLIGONUCLEOTIDE.

antisense oligonucleotides (AS-ODNs) Class of new therapeutics planned for the treatment of viral infections, autoimmune disease, endocrine disease and cancers; AS-ODNs are small synthetic molecules of single-stranded DNA that suppress gene expression by binding to RNA templates in a sequence-specific manner, thus suppressing gene expression, mRNA translation and therefore the production of disease-causing proteins; see GENE THERAPY, RIBOZYME.

antiseptic substance Compound which is designed for application to living tissues and which destroys a microorganism; see also MINIMUM INHIBITORY CONCENTRATION.

apheresis (Extracorporal) removal of potentially harmful compounds by technical devices; see PLASMAPHERESIS.

apitherapy Honey has been used for the treatment of wounds already 4,000 years ago; see also ALTERNATIVE MEDICINE.

apoptosis syn. cell death; see also INTEGRATIVE MEDICINE, TELOMER.

application Within the EC several categories of a. for marketing authorisation exist, each demanding a different documentation status, e.g. (categories of abriged a.): BIBLIOGRAPHIC, ESSENTIALLY SIMILAR and hybrid applications; see also ABRIGED APPLICATION, APPLICATION FEES, GENERIC APPLICATION, MARKETING AUTHORISATION HOLDER, PROPRIETARY MEDICINAL PRODUCTS, WELL-ESTABLISHED MEDICINAL USE.

application fee see MARKETING AUTHORISATION.

appointment log book see MONITOR'S VISIT LOG LIST.

approval Authorisation for marketing a new product; see also ACCELERATED APPROVAL PROGRAM, COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS, CONDITIONAL APPROVAL.

archiving According to EC guidelines, the following documents pertinent to a clinical trial have to be archived by the INVESTIGATOR for at least 15 years after completion of the trial: patient identification list, correspondence with the ethics committee and sponsor company, protocol including addenda/amendments, copies of CRFs (CASE RECORD FORMS); the SPONSOR has to archive the TRIAL MASTER FILE for lifetime of the product, reports 5 years beyond lifetime of the product; according to US regulations "an investigator shall retain records required to be maintained … for a period of 2 years following the date a MARKETING APPLICATION is approved for the drug for the indication for which it is being investigated; or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified"; hospitals are usually requested to archive data for 30 years, physicians with a private praxis for 10 years.

area under the curve (AUC) Area under the concentration/time curve of a substance in PHARMACOKINETIC investigations; describes the extent of the BIOAVAILABILITY of a drug.

assay Technique for measuring a biological response.

assessment report (AR) EC: "document exchanged between member states in the MUTUAL RECOGNITION PROCEDURE and which forms part of the opinion in the CENTRALISED PROCEDURE"; key document explaining why a MARKETING

AUTHORISATION and each of the proposed indications have been approved or rejected and detailing the risk-to-benefit considerations for the PRODUCT.

association study Investigates associations between one (independent) variable (e.g. the cause) and another (dependent) variable (e.g. the effect); useful statistical tests are e.g. odds ratio for NOMINAL DATA, Spearman's ratio for ORDINAL DATA, and Pearson's ratio for CONTINUOUS DATA.

as-treated analysis see ACTUAL-TREATED A., PER PROTOCOL A.

ATC exemption scheme Scheme similar to the CLINICAL TRIAL EXEMPTION scheme for animal health products.

attack rate def.: number of individuals exposed to a risk factor (or infection) who became ill compared with the number of individuals exposed to the risk factor (more correct: a proportion, not a rate; refers usually to infectious diseases); see also INCIDENCE, OUTCOME MEASUREMENT, PREVALENCE RATE, SECONDARY ATTACK RATE.

attributable risk see RISK.

audit Generally speaking, the purpose of an a. is to ensure that activities are performed in accordance with commonly accepted standards (GXP) and laws; in clinical research, an a. is the inspection of facilities, documentation and procedures of clinical INVESTIGATOR, SPONSOR, CONTRACT RESEARCH ORGANISATION, ETHICS COMMITTEE etc.; audits are made to ensure that either the internal system or a trial is performed in accordance with GOOD CLINICAL PRACTICE (GCP) and applicable laws, including ethical considerations as well as that RAW DATA and associated records have been accurately reported, and to establish whether practices were employed in the development of data that would impair their validity; audits are part of a QUALITY ASSURANCE system; audits or inspections usually start with an opening meeting and end with a closing/debriefing meeting (see EXIT INTERVIEW); types of a.: official external a. = INSPECTION by a supervisory authority, unofficial external a. = visit by a service company CONTRACT SERVICE ORGANISATION, CRO on request by the SPONSOR, unofficial internal a. = carried out by an internal structure (e.g. QUALITY ASSURANCE department, parent company) EC (III): "An internal a. independent of those participating in the trial should be conducted by or on behalf of the sponsor to assure the integrity of the QUALITY CONTROL system"; "the sponsor is responsible for conducting an internal a. of the trial" and for assuring "the investigators' acceptance of verification procedures, audit, and inspection"; a. are performed either as "during-study" a. or as "post-study" a.; usually the written final "Evaluation Report" reveals only findings e.g. deficiencies; an a. is not a scientific evaluation of the data of a study; a trial

audit is a comparison of raw data and associated records with the interim or final report; a regulatory a. is the verification of the credibility of data and the evaluation of the design, planning, conduct, monitoring and reporting of a CLINICAL TRIAL against regulatory requirements; further types of audits are: management a. = evaluates the efficiency and economy of a given operation in terms of accounting, purchasing, producing, personnel and research; program a. = evaluates effectiveness by a higher level of authority; a. can also be performed concerning other areas such as production plants, laboratory facilities or pharmacovigilance to ensure adherence to GOOD MANUFACTURING PRACTICE (GMP), GOOD LABORATORY PRACTICE (GLP) or GOOD PHARMACOVIGILANCE PRACTICE (GPhP) respectively; see also ACCEPTABLE QUALITY LEVEL, CONFIDENTIALITY, DATA QUALITY, ESTABLISHMENT INSPECTION REPORT, EXIT INTERVIEW, (CLOSING MEETING, DEBRIEFING MEETING), INSPECTION, ISO/DIS 10011–2, MEDICAL A.

audit certificate Document which certifies that an audit has taken place (to be stored together with the audit report in the TRIAL MASTER FILE); see also DATA TRAIL.

audit cycle Describes the frequency of audits; see AUDIT, AUDIT PLAN.

audit plan syn. AUDIT PROGRAM; term used to describe a listing of audit procedures to be performed in completing a single, specific audit ("agenda" to be followed when conducting an audit) as well as all audits to be executed over a particular period of time, e.g., 1 year/annual audit plan, with the scope of these audits and probable dates; the a.p. usually includes also various additional information such as person(s) responsible/lead auditor, planned budget, approver, etc.; see AUDIT, AUDIT CYCLE.

audit program see AUDIT, AUDIT PLAN.

audit trail Record of changes/deletions; see DATA TRAIL.

Austria Codex see NATIONAL DRUG LIST.

authorisation form Form used by the INVESTIGATOR and MONITOR to document that other persons than the investigator, e.g. a study nurse or a subinvestigator, are authorised to make entries or corrections in the CASE RECORD FORMS, or other critical trial-related procedures; see SUBINVESTIGATOR.

authorship According to the criteria formulated by the International Committee of Medical Journal Editors "authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published.

Conditions a, b, c must all be met" (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1991, 324: 1415–1417). Contributors are listed in the ACKNOWLEDGEMENTS (http://www.icmje.org/ethical_1author.html). See also PUBLICATION GUIDELINES.

autoimmune disease A disease in which the body produces antibodies against its own tissues; there are approx. 80 diseases known such as rheumatoid arthritis, systemic lupus erythematosus or autoimmune inflammatory bowel disease; see also GENETIC DISEASES, ORPHAN DISEASES.

autoimmunity Condition in which the body mounts an immune response against one of its own organs or tissues.

auxiliary medicinal product (AMP) Replaces the term non-investigational m.p. (NIMP); a medicinal product with a marketing authorisation (MA) valid throughout the European Community or in one or more Member States; in clinical studies, NIMPs should be supplied in the commercial available package and must be used according to the MA (otherwise it is a IMP); product liability applies; see INVESTIGATIONAL MEDICINAL PRODUCT.

average see WEIGHTED AVERAGE.

B

bacterium Any of a large group of microscopic, single-cell organisms with a very simple cell structure; some manufacture their own food from inorganic precursors alone, some live as parasites on other organisms, and some live on decaying matter.

balanced study Trial in which numbers of patients and their characteristics are equally distributed between groups e.g. similar number of males/females, above 65 years a.s.o.; see also STRATIFICATION.

balneotherapy Treatment with water rich in minerals such as sulfur, radon or other, usually in spas; see also ALTERNATIVE MEDICINE.

bar chart see GANTT CHART.

bar code Codification system using a number of vertical black lines the relative widths of which encode a specific information; used also for automated form reading by optical mark recognition; see also CODE.

baseline observation carried forward (BOCF) see LAST VALUE/LAST OBSERVATION CARRIED FORWARD.

baseline variables Characteristics of a patient and of his/her disease measured before the start (as soon as measurements are constant) of PROTOCOL treatment (baseline period); see also RUN-IN-PHASE; b.v. are important for the evaluation of the results of a CLINICAL TRIAL to avoid REGRESSION TO THE MEAN or LEARNING EFFECTS; see also DEMOGRAPHIC DATA, PLACEBO EFFECT.

batch syn. LOT; EC (IV): "a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous"; FDA: "specific quantity of a drug or other material that is intended to have uniform character and quality, within specific limits, and is produced according to a single manufacturing order during the same cycle of manufacture"; for stability testing batches should be

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selected at random, with not less than three batches to be taken for assessment of batch-to-batch variability; in order to be GMP-compliant a batch must have a minimal size of 100,000 units (e.g., vials; not applicable for investigational use during development); see also BATCH DOCUMENTATION, LOT, PILOT SCALE.

batch documentation EC: set of documents making possible to trace the history of the manufacture of a BATCH; b.d. needs to be retained for at least 1 year after the expiry date of the batch to which it relates or at least 5 years after the certification, whichever is longer; samples of each batch must be retained for at least 1 year after the EXPIRY DATE, samples of STARTING MATERIALS (other than solvents, gases and water) used must be retained for at least 2 years after the release of the product; see also FINISHED PRODUCT.

batch number EC (IV): "a distinctive combination of numbers and/or letters which specifically identifies a BATCH"; NLN: "a designation given by the manufacturer to a batch for the purpose of its identification".

batch recall see CLASS I (OR 2 OR 3) DEFECT.

batch release The release of a batch is the responsibility of the "Qualified Person"; a risk management plan must exist if batch release fails; see also QUALIFIED PERSON.

batch size see BATCH, PILOT SCALE.

Bayesian adverse reaction diagnostic instrument (BARDI) Bayesian based approach for assessing drug-induced illness; the goal is to calculate the posterior odds in favor of a particular drug being the cause of the adverse event; the posterior odds are calculated by considering six assessment subsets: "prior odds" as background epidemiological and clinical trials information, and five other dealing with case-specific information of possible differential diagnostic value ("likelihood ratios"); see also ADVERSE DRUG REACTION, PHARMACOVIGILANCE, SIGNAL DETECTION, STANDARDIZED ASSESSMENT OF CAUSALITY (SAC).

benefit-risk analysis see DECISION ANALYSIS, NUMBER NEEDED TO HARM, PERIODIC BENEFIT-RISK EVALUATION REPORT.

Berkson's bias There is an increased chance that hospitalised patients will have other comorbid conditions in addition to the disease of interest, compared with the decreased chance that non-hospitalised patients will have more than one condition; see also BIAS.

beta error syn. type II error; "missed difference"; statistical risk of saying there is no difference between two treatments A and B when actually there is one (error of falsely accepting the NULL HYPOTHESIS Ho; truth (ONE-SIDED): A>or<B, false judgment: A=B); therefore β is the probability of failing to detect, by mere chance,

a treatment difference at least as large as the degree specified (DELTA VALUE) by the ALTERNATIVE HYPOTHESIS Ha; 1-b is usually referred to as the POWER of the statistical test, the probability of detecting the specified difference and, therefore, the probability of rejecting Ho when Ha is true; the probability for a β-error increases with a lower delta, smaller SAMPLE SIZE and larger VARIANCE of the measured (continuous) VARIABLES; see also ALPHA ERROR, ERROR, GAMMA ERROR.

between-subject design opp. WITHIN-PATIENT D.; see DESIGN.

bias ERRORS due to incorrect assumptions (ICH E9: "systematic tendency of any aspect of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect to deviate from its true value"); frequent examples for bias are: recall b. = the more often a SUBJECT is asked the same question, the more likely are differences in the answer due to more intensive reflections or due to a better memory for findings which were important for the subject (which is not necessarily the case for controls, e.g. diagnosis or treatments in cancer); allocation b. = even drugs of the same substance class and being nearly identical may not be "allocated" by prescribing physicians in exactly the same way, new drugs are more likely to find their principle first uses in patients who have not responded satisfactorily to previously available drugs; attrition b. = biased occurrence and handling of protocol deviations and losses to follow-up; depletion b. = patients not tolerating or not responding to a treatment leave the study; changing pattern b. = methods of diagnosis, techniques, treatments a.s.o. may change over time; confounding b. = one or more variable associated, independently of exposure, both with exposure and outcome; detection b. = biased outcome assessment; performance b. = unequal provision of care apart from the treatment under investigation; publication (information) b. = studies with positive, statistically significant results are more likely to be published, which may result in overestimation of treatment results; reverse causality b. = study outcome preceded and caused actually the exposure; selection (sample distortion) b. = selected cases may not represent adequately the whole population or baseline characteristics may be different between two populations; principal b. reducing techniques are BLINDING and RANDOMIZATION; b. can also be induced by DROPOUTS because they rarely occur fully independent of the treatments being tested; see also BERKSON'S BIAS, DRUG CHANNELLING, ECOLOGICAL FALLACY, ERROR, HAWTHORNE EFFECT, IMMORTAL TIME BIAS, INTENT-TO-TREAT A., LABELLING PHENOMENON, LIFE EVENT DATA, NEYMAN FALLACY, PLACEBO EFFECT, PROTOPATHIC BIAS, REGRESSION PARADOX, SEQUENCE EFFECT.

bibliographical application EC: abridged application made by reference to published scientific literature; relevance and quality of these data should be stressed; see also APPLICATION.

binary outcomes see DATA.

bioactive compounds Extra-, non-nutritional components of food claimed to have beneficial health effects; normally, this does not include essential nutrients such as vitamins and unsaturated/essential fatty acids; many bc act primarily as ANTIOXIDANTS but their effect, often variable, is complex (e.g., hydroxytyrosol, one of many phenolics present in olives and olive oil; lycopene, a potent antioxidant carotenoid in tomatoes and other fruits; organosulfur compounds in garlic and onions; isothiocyanates in cruciferous vegetables; monoterpenes in citrus fruits, cherries, and herbs claimed to have anticarcinogenic actions and cardioprotective effects; there are rare reports of cases where processed components demonstrate a modified activity compared with the non-processed original herb, e.g., micronized water-soluble powder of green tea (Camellia sinensis, rich in epigallocatechin-3-gallate) interacted with an oral contraceptive causing acute hepatitis, probably via CYP3A4; see also ALTERNATIVE MEDICINE, FOOD SUPPLEMENT, FUNCTIONAL FOOD, MACROBIOTICS, NUTRIGENOMICS, ORTHOMOLECULAR MEDICINE, PHYTOMEDICINES, SELF-MEDICATION, TRADITIONAL HERBAL MEDICINAL PRODUCTS.

bioanalytical method Generating quantitative concentration data used for pharmacokinetic and toxicokinetic parameter, e.g., blood, plasma, serum, or urine; see ANALYSIS.

bioavailability EC: rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action; absolute b.: bioavailability of a given pharmaceutical form as compared with that (100 %) following intravenous administration; relative b.: bioavailability of a given pharmaceutical form administered by any route other than intravenous; b. is usually determined by blood level and/or urinary excretion data; examples of factors on which the b. depends are: disintegration-, dissolution rate, crystalline form, state of hydration, of ionisation, chemical stability in (gastric) fluids, surface area, presence or competition with food or drugs, drug binding to biological constituents as plasma protein or red blood cells, disease states, demographic characteristics (age, sex, race), FIRST-PASS EFFECT a.s.o.; see also ABSORPTION, DISSOLUTION TEST, FORMULATION, PHARMACOKINETIC, STEADY STATE STUDY, SUPRABIOAVAILABILITY.

biobank Repository of biological samples (usually human) for use in research like genomics and PERSONALIZED MEDICINE; biobanks are unique data sources for longitudinal studies; see also FRAMINGHAM STUDY.

bioburden Microorganisms (type, level) that can be present in raw materials or pharmaceutical products; if this exceeds a predefined level it is considered as CONTAMINATION; see also ACCEPTABLE DAILY INTAKE, IMPURITIES.

bioequivalence Equivalent doses of different dosage forms deliver the same amount of drug (e.g. 3×100 mg vs. 1×300 mg tablets); drugs whose rate and extent of absorption differ by ≤20 % (with the same BIOAVAILABILITY) are generally are considered as bioequivalent (acceptance range 0.80–1.25); FDA: "bioequivalent drug products means PHARMACEUTICAL EQUIVALENTS or pharmaceutical alternatives whose rate and extent of ABSORPTION do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose"; see also BIOLOGIC EQUIVALENT, DRUG COMPARABILITY STUDY, PHARMACEUTICAL EQUIVALENT, RULE 80/125, THERAPEUTIC EQUIVALENT.

bioinformatics The discipline encompassing the development and utilization of computational facilities to store, analyze and interpret biological data.

biologic equivalent Dosage form that results in similar BIOAVAILABILITY regardless of the pharmaceutical FORMULATION; see also ESSENTIALLY SIMILAR PRODUCT, PHARMACEUTICAL EQUIVALENT, THERAPEUTIC EQUIVALENT.

biological (medicinal) products Syn: "innovative biologics"; products prepared from biological materials of human, animal or microbiological origin such as vaccines, serums, toxins, ALLERGEN PRODUCTS or products derived from human blood or plasma; clinical trials with blood or biological products as well as their registration are subject to special regulations in order to assure absence of infectious contaminants (e.g. mandatory screening of blood donors); see also ADVANCED THERAPY, BIOPHARMACEUTICAL, BIOSIMILAR, ESTABLISHMENT LICENCE APPLICATION.

biological rhythm see CHRONOTHERAPY.

biomarker Def (NIH): "characteristic that is objectively measured and evaluated as an indicator of biologic processes, pathogenic processes or pharmacological response to a therapeutic intervention"; biomarkers can be used for detection, diagnosis, prediction or prognosis of diseases; examples: C-reactive protein (CRP) for inflammation, Prostate Specific Antigen (PSA) for diagnosing prostate cancer; elevated levels of IgE for predicting an allergy, homocysteine for cardiovascular risks, C-reactive protein (CRP), etc.; see also PROGNOSTIC/PREDICTIVE MARKER, PROTEOMICS, SURROGATE.

bionics Application of techniques in medical devices that mimic the biological functions; e.g., cardiac pacemakers which mimic the natural cardiac impulse generating system; see also DEVICE.

biopharmaceutical Therapeutic product involving biotechnology, e.g. genetic engineering; product of biotechnological origin such as antisense, genetic engineering, transgenics, involving manipulation of living organisms; this includes

among others also the post-translational modification for protein molecules, such as the addition of a carbohydrate moiety to a protein molecule ("protein glycosylation"); as sugar chains on glycoproteins can mediate biological activity, they influence safety and efficacy attributes; therefore, the relative amounts of the individual glycan structures must be monitored at all stages of research and development; see also BIOLOGICAL MEDICINAL PRODUCT, BIOSIMILAR, BIOTECHNOLOGY, INTERACTION OF DRUGS.

bioprosthesis Implantable device of non-synthetic, organic material; e.g., porcine heart valve; see also DEVICE.

biorepository see BIOBANK.

biosimilar Syn: "(bio-)generic", or "follow-on" biologic drug in contrast to "innovative biologics"; biologic drugs such as recombinant proteins, vaccines or antibodies produced by a competitor after expiry of patent protection are in the large majority of cases not absolutely identical to the reference drug and may vary e.g., in one or a few amino acids or exhibit post-translational modifications (such as glycosylation) depending on the cell line used and the culture conditions or simply the formulation to make the drug; such differences may or may not affect the properties as compared to the innovator (plasma levels, biological half-life, immunogenicity, bioactivity, side effects, …); thus a 100 % interchangeability may not always be given; market revenues have been estimated to $172 million in 2010; see also ESSENTIALLY SIMILAR PRODUCT, GENERIC.

biotechnology (Biotech) Development of products by a biological process. Production may be carried out by using intact organisms, such as yeasts and bacteria, or by using natural substances (e.g. enzymes) from organisms; techniques involving manipulation of living organisms or substances made by living organisms, particularly at the molecular genetic level; according to the U.S. Office of Science and Technology Policy, the term covers also "recently developed and newly emerging genetic manipulation techniques, such as recombinant DNA (rDNA), recombinant RNA (rRNA), and cell fusion, that are sometimes referred to as genetic engineering"; see also BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, GENETIC ENGINEERING, IMMUNOTHERAPY, TRANSGENIC DRUG, XENOTRANSPLANTATION.

birth control Methods considered to be highly effective (failure rate <1 % per year) are the following (ICH consensus guideline CPMP/ICH286/95): implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

birth date see DEVELOPMENT INTERNATIONAL BIRTH DATE, HARMONISED BIRTH DATE, INTERNATIONAL BIRTH DATE.

black list (1) List produced by the FDA which contains the names of INVESTIGATORS who are "ineligible to receive investigational products"

(Feb. 1993: 79 names, Sep. 2008: 114 names); an additional list contains the names of "investigators agreeing to some restriction of their use of investigational products" (Feb. 1993: 28 names, Sep. 2008: 14 names); in 1996, the "golden memory" of FÄPI, an unofficial black list of the German association of physicians in the industry (now DGPharMed), listed in the 1990s some 114 physicians, some named up to eight times; a similar referral system is run in UK for the ABPI; see also FRAUD, INVESTIGATIONAL DRUG; a "black list" is also under discussion in the EC for regulatory non-compliance of marketing authorization holders, mainly concerning pharmacovigilance aspects; other options for SANCTIONS include suspension or revocation of the marketing authorisation; (2) syn. NEGATIVE LIST; pharmaceutical products which cannot be prescribed either by brand name or generic name on the National Health Services; see also NEGATIVE LIST, POSITIVE LIST, REIMBURSEMENT.

black box warning Strongest warning the FDA requires, studies indicate a significant health risk for this particular drug; see also ADDITIONAL MONITORING, BLACK TRIANGLE.

black triangle A black triangle on SUMMARY OF PRODUCT CHARACTERISTICS indicates that the product is subject to INTENSIVE MONITORING for suspected ADVERSE REACTIONS (strongest form of warning of the FDA), often due to limited information available after start of marketing; see also ADDITIONAL MONITORING, BLACK BOX WARNING, PHARMACOVIGILANCE, PRESCRIPTION-EVENT MONITORING, YELLOW CARD SCHEME.

blinding syn. masking; to avoid BIAS in CONTROLLED CLINICAL TRIALS, treatment should be concealed from both patient and physician (double-b., doubly masked) or at least from one of them (single-b.) – most often from the patient; if treatment is also concealed from the evaluator (if not identical with the INVESTIGATOR) treatment allocation is triple-b. (also "treble b."); in some cases e.g. surgery, assessment of DEVICES, blind assessment of response may be the only practical way for blinding (partial b.); as a general rule, monitors and data management must be kept blind as well; blindness, however desirable, may not always be possible (tablets differing e.g. in taste and smell, obvious treatment/side effects, breaking of codes a.s.o.) especially for long lasting trials; the "weaker" the ENDPOINTS (i.e. the more likely results are influenced by the patient or physician) the more important will be adequate b.; in reporting ADVERSE EVENTS "there may be disadvantages to maintain b.: by retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily and notifying relevant parties in a blinded fashion is inappropriate and possibly misleading; breaking the blind for a single patient usually has little or no significant implications for the conduct of a clinical investigation or on the analysis of the final data (except when a serious or fatal outcome is the primary endpoint)" (ICH);

see also DISCLOSURE PROCEDURE, DOUBLE-DUMMY TECHNIQUE, EXPEDITED REPORTING.

block size Size of consecutive groups of patients in which RANDOMIZATION to treatments is balanced i.e. for each treatment the same number of subjects is foreseen; b.s. should not exceed 25 % of the total patient number and should also not be too small (<6) to avoid bias.

blood products see BIOLOGICAL PRODUCTS.

blue box requirements Additional information on labelling/package leaflet that may be required nationally in accordance with Articles 57 and 62 of Directive 2001/83/EC.

body composition The bc reflects the nutritional status; a person's weight consists of different components, basically fat and fat-free mass/lean body mass (which includes total body water, total protein, bones) that may be significantly altered in many disorders (e.g. burns, cachexia/wasting syndrome, congestive heart failure, dehydration, obesity, osteoporosis, renal-/liver diseases, trauma, etc.); methods for measuring the bc include as examples abdominal cross-sectional computerized axial tomography, bioelectrical impedance analysis, dual energy X-ray absorptiometry, magnetic resonance imaging (MRI) or positron emission tomography (PET); see also ANTHROPOMETRY, BODY MASS INDEX, WEIGHT.

body-mass-index (BMI) syn. Quetelet-Index; for estimating the ideal weight; BMI = body weight (in kg) divided by (height × height) (in square m) should be between (depending on age and sex) around 20–25; example: w = 76 kg, h = 1.82 m; 1.82 × 1.82 = 3.3; 76/3.3 = 23; common categories are: underweight <18.5, normal 18.5–24.9, overweight 25.0–29.9, obese 30.0 (according to others: obese ≥24 for women, ≥28 for men) and more; when compared to body scans and blood tests about ½ of the indices were wrong in obese women and ¼ in men; obesity can occur with a deficit in fat-free mass (mainly muscles) and with or without excess fat mass (sarcopenic obesity); see also ANTHROPOMETRY, BODY COMPOSITION, BROCA-FORMULA, LORENTZ-FORMULA, WAIST CIRCUMFERENCE, WAIST-HEIGHT-RATIO, WAIST-HIP-RATIO, WEIGHT.

body surface area (BSA) The body surface area (in m^2) can be calculated by various formulas e.g., the following formula of Du Bois and Du Bois: log a = 0.425 log w (body weight in kg) + 0.725 log h (body height in cm) – 2.144; the standard value for a man with 70 kg and 180 cm is 1.73 m^2. A simplified formula, only valid for well-proportioned infants and children between the weights of 3 and 30 kg, is the following: BSA = (Wt. + 4)/30, weight being in kilograms and BSA being in square meters; see also ANTHROPOMETRY, MOSTELLER FORMULA, THERAPEUTIC INDEX.

body water The body water is about 60 % of the body WEIGHT, approximately 42 L in an average 70-kg adult (plasma volume 3 L, blood volume 5.5 L, extracellular fluids outside plasma 12 L); higher values of b.w. are found in infants (77 %) and lower in ELDERLY subjects; see also ADME, GERIATRIC EVALUATIONS.

body weight see BODY-MASS-INDEX, BODY SURFACE AREA, BROCA-FORMULA, LORENTZ-FORMULA, WEIGHT.

Bonferroni correction In order to avoid ERRORS by repeated significance testing the SIGNIFICANCE LEVEL is divided by the number of comparisons ("Hochberg correction"; e.g. if five analyses are done the significance level should be 0.01 i.e. 0.05/5); more correct, the ALPHA (type I) ERROR rate increases, if a P-VALUE of 5 % is accepted, after 5 independent and repeated tests to: $(1-(0.95)5)=0.2262$ or 23 %; the B. inequality states that the experiment-wise error rate cannot exceed the sum of the error rates of each test considered individually; apart from the B. correction, other formula for corrections for multiple tests exist; see also INTERIM ANALYSIS, PRIMARY ENDPOINT, WEI-LACHIN PROCEDURE.

botanical drug product see PHYTOMEDICINES.

boundary value Value that corresponds to a minimum or maximum value specified for a VARIABLE.

box-score review A review that differentiates between treatments by comparing the treatment modality's proportion of positive findings vis-à-vis the total number of studies for that modality; see also META-ANALYSIS, NARRATIVE REVIEW.

Braille system A 6 dot system devised by Louis Braille in 1821 and that allows blind people to read texts; outer packages of medicinal products intended to be used by patients must identify the product written in "Braille" since 2006; each character should be at least 6 mm high and 4 mm wide; see also LABELLING.

brand name Usually based on a registered trade mark; see also TRADE NAME.

bridging study Agreement between ICH-countries: Phase I pharmacokinetic data generated anywhere in the three main regions of ICH, Japan and Asia Pacific, Europe and the USA are acceptable, as long as it can be demonstrated that the pharmacokinetic behaviour of the drug is the same; a similar bridging approach is applicable for paediatric indications, if it can be demonstrated that pharmacokinetics in children are essentially the same as in adults.

British Approved Name (BAN) see INTERNATIONAL NON-PROPRIETARY NAME.

Broca-formula formula used for calculating the "ideal weight": height (cm) – 100 = ideal weight (kg); see also BODY MASS INDEX, LORENTZ FORMULA, WEIGHT.

bug error (fault) in a software; see also ERROR.

bug log List of problems encountered with a system; it includes date/time of problems, origin, corrective measures taken, etc.; see also COMPUTERISED SYSTEM.

bulk drug substance see BULK PRODUCT.

bulk product EC (IV): "any product which has completed all processing stages up to, but not including, final packaging" (i.e. pharmacologically active component of a DRUG before formulation); see also FINISHED PRODUCT, INTERMEDIATE PRODUCT, MEDICINAL PRODUCT, PACKAGING.

byproducts see EXCIPIENTS, FORMULATION, IMPURITY.

C

cachexia def. unintended and progressive weight loss that is often accompanied by weakness, fever, nutritional deficiencies, diarrhoea, and usually with a disproportionate muscle wasting. It occurs in many chronic illnesses and diseases such as cancer, in particular advanced stage cancer, but also Alzheimer's disease, chronic heart failure, chronic lung disease, congestive heart failure, cystic fibrosis, Crohn's disease, renal failure, rheumatoid arthritis, tuberculosis, liver cirrhosis, heart surgery, sepsis and sarcopenia; there is no universally accepted definition but the 95 % CIs for change in body weight in healthy adults is ±2 % in 1 month and ±5 % in 6 months; see WEIGHT.

calibration EC (IV): "the set of operations which establish, under specified conditions, the relationship between VALUES indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard".

CAMA Computer assisted marketing authorisation (Europe), whereby the information on the new DRUG is submitted in electronic form; see CANDA.

Canada Vigilance Program Canada's reporting program for adverse reactions; similar programs are the "EUDRAVIGILANCE Program" (EC) and "MEDWATCH" (FDA).

CANDA Computer assisted new drug application (US), whereby the information on the new DRUG is submitted in electronic form, e.g. on optical disks of WORM – type (write once, read many); no universal recommendations exist at the time being; see also DAMOS.

CAPA see CORRECTIVE AND PREVENTIVE ACTIONS.

Capability Maturity Model (CMM) According to the "Capability Maturity Model" there are five maturity levels: (1) Initial: The software process is

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characterised as ad hoc, and occasionally even chaotic; few processes are defined, and success depends on individual effort and heroics. (2) Repeatable: Basic project management processes are established to track cost, schedule, and functionality; the necessary process discipline is in place to repeat earlier successes on projects with similar applications. (3) Defined: The software process for both management and engineering activities is documented, standardised and integrated into a standard software process for the organisation; all projects use an approved, tailored version of the organisation's standard software process for developing and maintaining software. (4) Managed: Detailed measures of the software process and product quality are collected; both the software process and products are quantitatively understood and controlled. (5) Optimising: Continuous process improvement is enabled by quantitative feedback from the process and from piloting innovative ideas and technologies.

CAPLA Computer assisted product license application; see CANDA.

CAPLAR Computer assisted product licensing application review (USA); see CANDA.

carcinogen Cancer-causing agent; see ALIMENTARY RISKS.

carcinogenicity tests Such t. are normally required for substances likely to be applied in man longer than 3 months or having a close chemical analogy with known (co-)carcinogenic compounds or in respect to substances which showed suspicious changes in longterm toxicological, mutagenicity or other short term tests; typical tests may require e.g. 500 rats exposed over 24 months; see TOXICITY TESTS.

cardiac index Hemodynamic parameter (L/min)/(m^2); normal values: 2.6–4.2 L/min; see also EJECTION FRACTION.

carry-over effect see SEQUENCE EFFECT.

carrier-based drug delivery see DRUG DELIVERY SYSTEMS, FORMULATION.

case-control study Retrospective study which investigates, from outcome to exposure, potential associations between a drug and ADVERSE EVENTS or, more generally, between a variable and the onset of a DISEASE; a study in which patients who already have a certain condition are compared to people who do not. E.g.: lung cancer patients are asked how much they smoked in the past; answers are then compared with a sample of the general population; c.c.s. are often the design of choice when outcome is rare and when random sampling is therefore far less efficient than selection by outcome; the use of a drug by patients with a specific disease ("cases") is compared with that of a group of patients without the disease but otherwise similar (the "controls");

if use is higher among cases than controls, then it may be possible to infer an association between the drug and the disease; example: subjects suffering from lung cancer are selected as "cases" and another group of non-diseased subjects as the "controls"; than the frequency of smokers in both groups is determined in order to clarify a relationship between smoking habits and lung cancer (in a COHORT STUDY one would draw a sample of smokers and non-smokers and compare the frequency of lung cancer); advantages: smaller number of patients, shorter duration, reduced costs; can elucidate risk factors; useful when there is considerable latency between use of drug and emergence of ADVERSE EVENTS; disadvantages are BIAS as: selected cases may not be representative but a specific subgroup (e.g. hospitalised and with a more severe form of disease), the controls may not be identical to cases in any way other than the absence of disease, collection of data on preceding drug use may be biased (e.g. women with breast cancer may be more aware of their previous use of oral contraceptives than non-breast cancer patients); the method for choosing the control group should always be established before the study begins; it may also be useful to select an additional control group from the general population to reduce the likelihood of false conclusions; see also COHORT STUDY, CROSS-SECTIONAL STUDY, DESIGN, NESTED CASE-CONTROL STUDIES. The ODDS RATIO (relative risk) is calculated as follows:

Exposure	Disease YES (cases)	Disease NO (controls)
Yes	a	b
No	c	d
Odds of exposure	a/c	b/d

case crossover see SINGLE CASE STUDY.

case-fatality rate Number of subjects who die of a specific disease, within a given number of person-years of follow-up, divided by the number of subjects developing this disease (more correct: a proportion, not a rate); see also LETHALITY, PREVALENCE RATE.

case record form see CASE REPORT FORM (CRF).

case report form (CRF) syn. case record form, DATA collection form; record of data or other information on SUBJECTS in a CLINICAL TRIAL as defined by the PROTOCOL; data may be recorded by hard (e.g. NCR (NO CARBON REQUIRED) paper) copies, electronic/web-based or optical disk methods or any other means, ensuring accurate input and allowing verification against RAW DATA; CRFs are essential documents; EC: "CRFs may be requested by Member States and should therefore always be available"; CRFs must be archived as long as the product is on the market; see also DATA TRANSFER, ELECTRONIC CRF, ELECTRONIC DATA, PATIENT DIARY, RAW DATA.

case series Study of case patients only; there are no control subjects; see DESIGN.

case-surveillance Study of patients with diseases which are likely to be caused by drug exposure; see also POST-MARKETING SAFETY STUDY, POST-MARKETING SURVEILLANCE.

categorical data see DATA, VISUAL ANALOGUE SCALE.

causality syn. imputability; in many countries (e.g. US, France) a c. assessment of ADVERSE REACTIONS, in addition to REPORTS, is mandatory; in Germany, but also within the EC, a c. assessment is currently not obligatory, despite that a classification system with three categories has been adopted by the member states ("A – probable": reasons and documentation given are sufficient to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable; "B – possible": information in the report is sufficient to accept the possibility of a causal relationship, in the sense of not being impossible or unlikely, although the connection is uncertain or doubtful, because of, e.g. missing data or poor documentation; "O – unclassified": reports where causality is, for one reason or another, not assessable, e.g. because of insufficient evidence, poor documentation or conflicting data); a frequently used classification system is that according to KARCH and Lasagna: definite = adverse reaction (ADR) that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues, that follows a known response pattern, that is confirmed by DECHALLENGE and RECHALLENGE; probable = ADR as above but that has not been confirmed by rechallenge and that could not be reasonably explained by the known characteristics of the patient's clinical state; possible = ADR that follows a reasonable temporal sequence from administration, a known response pattern, but that could have been produced by the patient's clinical state or other modes of therapy; conditional = ADR as above but that does not follow a known response pattern to the suspected drug and that could not be reasonably explained by the patient's clinical state; doubtful = any reaction that does not meet the criteria above; insufficient = there is insufficient data available to make a comment; categories of the WHO are also widely used: Certain – reasons and documentation given are sufficient to be sure of a causal relationship (e.g. same reaction on re-exposure); Probable – reasons and documentation given are sufficient to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable; Possible – information in the report is sufficient to accept the possibility of a causal relationship, in the sense of not being impossible or unlikely, although the connection is uncertain or doubtful; Impossible/Unrelated – no reasonable temporal sequence from administration of the drug; event is clearly produced by the patient's clinical state or other modes of therapy; Unclassified/

Unassessable – reports where causality is, for one reason or another, not assessable, e.g. because of insufficient evidence, poor documentation or conflicting data; the French Ministry of Health demands use of an own, five-point causality assessment method; in order to reduce inter-rater VARIANCES which occur when c. assessment is done by ante mortem methods STANDARDIZED DECISION AIDS (SDA) have been developed; see also DRUG INTERACTION PROBABILITY SCALE, NARANJO NOMOGRAM, STANDARDIZED ASSESSMENT OF CAUSALITY.

ceiling effect opp. FLOOR EFFECT; treatment effects or scores (e.g. grip strength) that can be reached are limited, even when dosage or treatment duration a.s.o. is increased (e.g. analgesics); results will be heavily skewed (see SKEWNESS).

cell The smallest structural unit of living organisms that is able to grow and reproduce independently.

cell culture Growth of a collection of cells, usually of just one genotype, under laboratory conditions.

cell cycle The term given to the series of tightly regulated steps that a cell goes through between its creation and its division to form two daughter cells.

cell line Cells which grow and replicate continuously in cell culture outside the living organism.

cell therapy see ADVANCED THERAPY.

cellular reprogramming syn. Dedifferentiation; techniques to convert differentiated cells to a pluripotent state (see also ADVANCED THERAPY, REGENERATIVE MEDICINE, STEM CELL THERAPY).

CE marking (of a MEDICAL DEVICE) The CE marking of conformity must appear in a visible, legible and indelible form on the device or its sterile pack (where practicable and appropriate), and on the instructions for use. where applicable, the CE marking must also appear on the sales packaging. The CE marking must be accompanied by the identification number of the notified body responsible for implementation of the respective quality and conformity procedures; for devices which are custom-made or devices intended for clinical investigations special regulations will be established; these devices do not bear the CE marking; see also EC TYPE-EXAMINATION CERTIFICATE.

censored data Values which are not known at the time of analysis, but which have a known minimum value (e.g. survival).

central ethics committee syn. Lead Ethics Committee; ETHICS COMMITTEE reviewing a PROTOCOL for different institutions, e.g. in a multicentre or

multinational trial; in the EU the vote of one EC per country is (legally) sufficient, frequently however, the formal approval by the ethics committee of each participating hospital is requested in addition; in other countries, e.g. France, approval by one central e.c. is sufficient.

centralised procedure former: CONCERTATION PROCEDURE, former high technology procedure; mandatory procedure in the EC for getting marketing authorization for all biotechnology products (products developed by recombinant DNA technology, monoclonal antibody methods, gene and cell therapies, etc.), optional for other biotech products and new chemical entities (products of significant therapeutic interest or innovation); presentation to the COMMITEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) is a must unless the application is accompanied by a signed declaration that no other application has been made during the preceding or will be made during the next 5 years resp.; presentation to the EUROPEAN MEDICINES (EVALUATION) AGENCY (EMEA now EMA) and CPMP resp. is undertaken by the company, the RAPPORTEUR member state will be appointed by the CPMP after discussion with the company; the CPMP has 210 days for examination and to reach its opinion which is then send to the Commission, member states and the applicant, including the assessment report, the SUMMARY OF PRODUCT CHARACTERISTICS, the LABELLING and the PACKAGE INSERT; the Commission has then 30 days for decision, after which the member states have 28 days for raising questions; then the application goes to the standing committee (with representatives from the member states) and becomes a final Commission's decision if the majority is in favour; the total time to approval should be max. 300 days, the final decision will be binding for all member states; products will automatically benefit from a 10 year period of protection of innovation against use of the submitted data by second parties in the event of there being no effective patent cover; see also DECENTRALISED PROCEDURE.

certificate of destruction Unused or returned medication is usually destroyed either by the sponsor or by the hospital pharmacy; for DRUG ACCOUNTABILITY reasons this process has to be documented with date, quantity, and identification of drugs incl. the BATCH NUMBER.

certified copy see ELECTRONIC DATA.

cessation of placing on the market By analogy to PLACING ON THE MARKET, cessation of placing on the market/cessation of release into the market means that the product is no longer available for supply; the date is the date of the last release into the distribution chain and should be notified 2 months in advance (Reg_2004_726); there are no fixed rules for the frequency of PSURs after (voluntary) withdrawal of a product; this is decided by the CA on a case-by-case basis; see also WITHDRAWAL.

challenge agent a pharmaceutical product that is given to subjects to produce a physiological response that is necessary before the pharmacological action of the medicinal product can be assessed.

changing pattern see BIAS, CUSUM PLOT.

chemical equivalents see PHARMACEUTICAL EQUIVALENTS.

chemokins Biological substances acting as chemo-attractants, e.g. such as eotaxin which attracts eosinophils.

chemosensitizer Substance with modulatory activities on MULTIDRUG RESISTANT cells; the magnitude of it's effect is described by the ratio of the IC50 value for a cytotoxic drug in the absence and presence of a non-toxic, fixed concentration of the chemosensitizer.

chirality Drugs with a carbon atom to which four different other atoms bind (asymmetric carbon atom) can exist in two different, nonsuper-imposable stereochemical versions (STEREOISOMERS, ENANTIOMERS), similar to mirror images of each other, and which show under suitable conditions optical activity (i.e. ability to rotate the plane of plane-polarized light in a polarimeter either to right "R" or to left "S"); biological systems usually produce only one version, e.g. L-AMINOACIDS; chemical synthesis, however, results in 50:50 mixtures of both types of stereoisomeres, so called racemates; there are many examples that L- and D-forms can act differently in organisms (e.g. D-aminoacids are usually toxic in contrast to L-forms which may be even essential for life, L-sotalol is a β-blocker whereas D-sotalol is an anti-arhythmic, L-thyroxin is a hormone whereas D-thyroxin is a lipid-lowering substance, D-albuterol is an antiasthmatic but L-albuterol increases intensity of asthmatic bronchospasms; only R-thalidomid causes embryotoxic effects, the L-form produces a sedative effect, a.s.o.); it is still unclear to which extent this aspect may be important also for other drugs; health authorities (e.g. FDA) may request studies with the racemate as well as with the isomers; however there exist also examples where the racemate has synergistic properties (e.g. tramadol in analgesia) or where the enantiomer has been found to be inverted by the human organism to the racemate (e.g. L-thalidomid); see also DISTOMER, ENANTIOMER, EUTOMER.

chromosomes Subcellular structures which convey the genetic material of an organism; threadlike components in the cell that contain DNA and proteins; genes are carried on the chromosomes; see also GENE, NUCLEOTIDE, TELOMER.

chronic toxicity Toxic effects on a organism after continuous or repeated exposure; see TOXICITY.

chronotherapy Treatment optimising desired effects and minimising undesired ones by administering medications at the appropriate time according to the body's biological rhythms, e.g. administration of methyl-prednisolon in the morning, asthma and heart medication in the morning as attacks are peaking in early morning, duodenal ulcers have shown to peak in May-June and November-December; signs and symptoms of many diseases vary over a 24-h period, e.g. asthma symptoms may be more than 100-fold greater during sleep, myocardial infarction is more frequent during the initial hours of activity, hypertension is most prominent around noon, ulcer disease is worsening during early hours of sleep; in cancer treatment, hypothesis of chronotherapy is that normal tissues conform to a circadian growth cycle, while malignant cell divisions occur randomly; see also CIRCADIAN RHYTHM.

CIOMS International, non-governmental, non-profit organisation, which was set up in 1949 under the auspices of the WHO and UNESCO; its prime functions include acting as sound board for capturing and disseminating informed opinion on new developments in biology and medicine, and to explore their social, ethical, moral, administrative, and legal implications.

CIOMS I form Reporting form for adverse reactions; as a minimum they should contain the following information: identifiable source, patient identification, a suspect drug, a suspect reaction; manufacturers should submit completed CIOMS (COUNCIL FOR INTERNATIONAL ORGANISATION OF MEDICAL SCIENCES) report forms to regulatory authorities as soon as they are received but not later than 15 working days after their receipt; this period begins as soon as a company, or any part or affiliate of a company, receives the report; many regulatory authorities including of Eastern Europe accept this format for reporting, e.g. Australia, France, Italy, Poland, Russia, Slovenia, United Kingdom; see also ADVERSE DRUG REACTION.

circadian rhythm Functional cycle of cells and organs conforming to 24-h cycle of activity; see CHRONOTHERAPY.

citation style many journals use the "AMA Citation Style" (American Medical Association Manual of Style, 9th edition), examples: (Book) Okuda M, Okuda D. Star Trek Chronology: The History of the Future. New York: Pocket Books; 1993. (Journal or Magazine Article – with volume numbers) Wilcox RV. Shifting roles and synthetic women in Star trek: the next generation. Stud Pop Culture. 1991;13:53–65. (Newspaper, Magazine or Journal Article – without volume numbers) Di Rado A. Trekking through college: classes explore modern society using the world of Star trek. Los Angeles Times. March 15, 1995:A3. (Encyclopedia Article) Sturgeon T. Science fiction. In: Lorimer LT, editorial director; Cummings C, ed-in-chief; Leish KW, managing ed. The Encyclopedia Americana. Vol 24. International ed.

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class 1 (or 2 or 3) defect see PRODUCT DEFECT, QUALITY DEFECT.

classification of recurrence Classification system used for describing recurrence of tumors after therapy: a = alive, without recurrence, B = alive with recurrence, C = alive, recurrence unknown, D = dead without recurrence, E = dead with recurrence, F = dead, recurrence unknown, G = lost, without recurrence; see also TUMOR STAGING.

clastogen Substance causing toxic effects upon genetic material (chromosomes) of cells, inducing permanent and transmissible damages with microscopically detectable structural alterations of chromosomes; see also ANEUGEN, GENOTOXICITY, TOXICITY TESTS.

clean area EC (IV): "an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce

the introduction, generation and retention of contaminants within the area"; see also CROSS CONTAMINATION.

clearance (Cl) Rate of drug elimination from the body (volume of blood cleared of a drug per minute: Cl = 0.693 (Vd)/(t½) = ml/min) where the VOLUME OF DISTRIBUTION (Vd) is expressed in ml/kg and the HALF-LIFE (t½) in minutes or hours; see also CREATININE CLEARANCE, ELIMINATION, PHARMACOKINETIC.

clerical error syn. key-punch ERROR; c.e. are mainly those of transferring information, e.g. person or instrument to document, document to punch cards or computers, computer output to reports, typing mistakes a.s.o.; see also BIAS.

climatic zones As the stability of a medicinal product may vary in dependence of climatic conditions, four climatic zones have been defined; see also IMPURITY, STABILITY TEST. Test conditions are usually 21 °C/45 % r.h., 25 °C/60 % r.h., 30 °C/35 % r.h., 30 °C/70 % r.h. (relative humidity).

	I	II	III	IV
Mean annual temperature (open air) (°C)	up to 15	>15–22	>22	>22
Calculated mean annual temperature (°C)	up to 20.5	>20.5–24	>24	>24
Mean annual water vapour partial pressure (mbar)	up to 11	>11–18	up to 15	>15

clinical development plan Plan for clinical development of a new drug, from first application in man to drug registration; such a plan usually includes e.g.: overview of the therapeutic indication(s), target product profile, profile of competitive drugs, properties of the new substance, justification for development, advantages and risks, overview of principal clinical trials with design and size, drug supplies, staffing requirements and financial resources; see STUDY LIST.

clinical heterogeneity C.h. results mainly from differences in characteristics of patients such as age, gender, genetic/ethnic differences, co-morbidities, disease severity etc. and may be responsible for considerable VARIABILITY of results or conclusions; in an attempt to reduce c.h. CLINICAL TRIALS define SELECTION CRITERIA; see BIAS, CONFIDENCE INTERVAL, ERROR; see also HEALTH CARE SERVICES, MEDICAL CULTURE, META-ANALYSIS, PRESCRIPTION.

clinical hold FDA: "A c.h. is an order issued by FDA to the SPONSOR to delay a proposed clinical investigation or to suspend an ongoing investigation."

clinical investigation see CLINICAL TRIAL.

clinical investigation plan (CIP) see PROTOCOL.

clinical program outline see STUDY LIST.

clinical research assistant (CRA) see CLINICAL RESEARCH ASSOCIATE.

clinical research associate (CRA) syn. clinical research assistant; person performing mainly the "on-site" monitoring activity of a trial; also called "home based CRA" or local CRA if based outside of the office of a company; some of these activities may be also delegated to a "STUDY NURSE"; see also MONITOR.

clinical research coordinator (CRC) see CLINICAL TRIAL COORDINATOR, STUDY COORDINATOR.

clinical research executive (CRE) Member of the clinical research staff, e.g. a MONITOR.

clinical research manager (CRM) syn. clinical trial manager; responsible person for a clinical project, including the supervision of monitoring; nominated by the sponsor; see also CLINICAL TRIAL COORDINATOR.

clinical research organisation (CRO) see CONTRACT RESEARCH ORGANISATION.

clinical significance see DELTA VALUE.

clinical study Any clinical investigation involving human subjects; see CLINICAL TRIAL.

clinical trial (CT) syn. clinical investigation, clinical study; "any systematic and carefully designed study on medicinal products in human SUBJECTS whether in patients or non-patient volunteers"; CTs are usually subject to an authorisation; some consider the term "CLINICAL STUDY" as a broader term that includes post-authorisation activities other than PHASE IV trials; the aim of a CT is to discover or verify the effects of, and identify any ADVERSE REACTION to (investigational) products and to study their absorption, distribution, metabolism and excretion in order to ascertain the EFFICACY and safety of the product; a CT can be either prospective (non-randomized observational COHORT, RANDOMIZED CONTROLLED – frequently double-BLIND –, WITHDRAWAL, RECHALLENGE, etc.) or retrospective (historical control, CASE-CONTROL study, CROSS-SECTIONAL study); activities concerning CTs are usually divided into four stages: a planning or set-up phase, requiring about a few weeks to several months for protocol and CASE RECORD FORM preparation, packaging, labelling and regulatory review incl. by an ETHICAL COMMITTEE, a patient treatment or MONITORING phase (including follow-up) and finally the analysis as well as the reporting phase, requiring also a few weeks to several months

for DATA clean-up, QUALITY ASSURANCE, statistical ANALYSIS and REPORT writing; average costs for clinical trials per drug were estimated to US$ 22.4 mio the late 1990s; administrative workload and costs for CT-authorisations is estimated to be twice as high in 2010 compared to the time prior Dir 2001/20/EC; in parallel, the number of clinical trial in the EU has decreased by 25 % from about 5,000 in 2007 to 3,800 in 2011; see also COSTS, DESIGN, INVESTIGATIONAL MEDICINAL PRODUCT, MEDICAL OFFICE TRIAL, MEGATRIAL, MULTICENTRE TRIAL, NON-ALPHA SITE, POSTMARKETING SURVEILLANCE, RUN-IN PHASE, SOLICITED REPORT.

clinical trial authorisation (CTA) Formal approval to do studies; in most countries formal approval by health authorities to do studies esp. with experimental drugs is requested (in particular for genetically modified organisms or the very first application of a new drug in man), e.g. most countries in Eastern Europe; in the EC, a formal process exists that includes the entry of trial details in the "EUDRACT" database and notification to the competent authorities (CA); a tacit authorization is granted if the CA has not informed the sponsor within 60 days of any grounds for non-acceptance; many CA request the payment of a fee around € 1,500 for authorisation; other countries have less strict regulations and only notification to the health authority is necessary, e.g. Australia, Germany a.s.o.; see also CLINICAL TRIAL CERTIFICATE, CLINICAL TRIAL DATABASE, CLINICAL TRIAL EXEMPTION, EUDRACT.

clinical trial certificate (CTC) Formal approval to do studies in the UK; valid for 2 years, renewable; see also CLINICAL TRIAL AUTHORISATION, CLINICAL TRIAL EXEMPTION.

clinical trial compensation guidelines Guidelines produced by the ABPI; according to which compensation should be paid when the injury was attributable to the medicinal product or any procedure provided for by the protocol, for the more serious injury of an enduring and disabling character (not for temporary pain or discomfort), for injuries caused by procedures adopted to deal with adverse reactions to a product under trial, regardless of whether the reaction was foreseeable or predictable or whether the patient is able to prove negligence of the company; see also INSURANCE.

clinical trial coordinator (CTC) syn. clinical coordinator, trial c., study c., research c.; in large and complex trials it may be suitable to nominate a person acting as liaison between sponsor and investigator and for administrative responsibilities, e.g. who coordinates dates for visits, investigations a.s.o. but reviews also data and records before monitor's visit; see also CLINICAL RESEARCH MANAGER, STUDY COORDINATOR, STUDY NURSE.

clinical trial data base (CTDB) Public data base that lists planned or ongoing clinical trials; editors of biomedical journals request that a clinical trial

has been listed in a CTDB in order to be considered for publication (International Committee of Medical Journal Editors, ICMJE: Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication; updated October 2007); the WHO hosts a web-based platform, the International Clinical Trials Registry Platform, ICTRP (http://www.who.int/ictrp/en/) or the ENCePP Inventory of Databases (http://www.encepp.eu/encepp/resourcesDatabase.jsp); accepted databases are: www.actr.org.au, www.clinicaltrials.gov, www.ISRCTN.org, www.umin.ac.jp/ctr/index/htm, www.trialregister.nl and of the EU (CTR, https://www.clinicaltrialsregister.eu/, since March 2011); the "Pharmaceutical Research and Manufacturers of America" (PhRMA, www.phrma.org) maintains a clinical study database that includes summaries of unpublished study results; see also DATA BASE, EUDRACT.

clinical trial exemption (CTX) Exemption from the need to gain formal approval to perform clinical studies in the UK; see also CLINICAL TRIAL AUTHORISATION, CLINICAL TRIAL CERTIFICATE.

clinical trial manager see CLINICAL RESEARCH MANAGER.

clinical trial manual see TRIAL MASTER FILE.

clinical trial notification (CTN) see CLINICAL TRIAL AUTHORISATION.

clinical trials register see CLINICAL TRIAL DATABASE.

clinical trial report see REPORT.

clinical trial status report Gives (in case of a multicentre trial for each centre) the current status of a particular trial, including details on the number of patients recruited/completed/lost, serious adverse events, a.s.o.; see also REPORT.

clinical trial supplies Test and comparator substances for a specific trial, usually produced and labelled by the production unit of the sponsor company; in some countries there exist specific regulations for importation of test drugs; see also BLINDING, DOUBLE-DUMMY TECHNIQUE, LABELLING.

clone A group of genes, cells, or organisms derived from a common ancestor. Because there is no combining of genetic material (as in sexual reproduction), the members of the clone are genetically identical or nearly identical to the parent.

cloning Technique of reproducing organisms with identical properties; cloning of animals involves replacing the nucleus of an embryo with that of a cell of another animal; see also GENE THERAPY.

close down see TERMINATION VISIT.

closed system opposite to open system; FDA: "computerized system whereby access is controlled by persons responsible for the content of ELECTRONIC RECORDS that are on the system"; see also COMPUTERISED SYSTEM, ELECTRONIC SIGNATURE, OPEN SYSTEMS.

close out visit see TERMINATION VISIT.

closing meeting see AUDIT, EXIT INTERVIEW.

cloud systems Network-based systems that allow remote access to "everything and everywhere" (e.g., mobile phones with access to internet, company server, retrieval and storage of data, fax, GPS, etc.); such systems are usually customer-tailored.

clusters Occurrence of "more cases than expected" in space and time which may indicate that an etiological factor was introduced into the environment; see also INCIDENCE RATE.

cluster randomized controlled clinical trial Syn. group-randomized controlled clinical trial; design where clusters of subjects are randomized instead of individuals; such designs can comply for treatment conditions that cannot easily be influenced, e.g. specific lifestyles or medical cultures; see DESIGN.

coating see FILM COATING.

Cockcroft formula see CREATININE CLEARANCE.

code Numeric value assigned to textual data; e.g. for diagnoses: SNOMED (of the College of American Pathologists), ICD-9 C., ICD-10 C., READ CLINICAL CLASSIFICATION for diagnoses, signs, symptoms and history; for ADVERSE EVENTS: WHO-ADVERSE REACTION TERMINOLOGY/WHO-ADVERSE REACTION DICTIONARY or FDA's COSTART (Coding System for a Thesaurus of Adverse Reaction Terms); for coding medications or treatments resp.: WHO-DRUG DICTIONARY and DRUG REFERENCE LIST resp., WHO-International Nonproprietary Names for Pharmaceutical Substances Classification, Nutley System Glossary c., ANATOMICAL THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM (ATC), and its derived EPhMRA system, the Aberdeen Drug Coding System, International Classification of Primary Care, ICDA, MEDICAL DICTIONARY FOR DRUG REGULATORY ACTIVITY (MEDDRA) a.s.o.; electrocardiograms can be classified according to the MINNESOTA C., malignant diseases by the ICD-O and so on; outcome is also often codified separately, e.g. as: ADVERSE EVENT, treatment failure, early improvement, refused treatment, death during study, lost to follow-up, did not cooperate, PROTOCOL violation, entry violation, intercurrent illness, completed according to protocol a.s.o.; in software development processes coding is the software activity where the detailed design specification is implemented as source code; coding is the

lowest level of abstraction for the software development process (FDA: Gen. Principles of SW Validation); in medicine, subjects data can be "identified" (e.g., by security or health insurance number) "single coded", "double coded" or "anonymised", depending whether the respective subject can be directly identified, indirectly via a single code key or two sets of code keys that are kept by two different parties, or not at all because the link between code(s) and the identity has been deleted; coding dictionaries used should always be specified in reports such as the PBRER.

code breaking procedures see DISCLOSURE PROCEDURE.

codes of practice In order to harmonise activities of public interest the pharmaceutical industry has issued a number of voluntary and self-limiting regulations e.g. the CLINICAL TRIAL COMPENSATION GUIDELINES, the "Code of Practice for the Clinical Assessment of Licensed Medicinal Products in General Practice", issued by the ABPI (UK), or the IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES.

codon a sequence of three nucleotide bases in a DNA or RNA molecule that in the process of protein synthesis codes for one amino acid or provides a signal to stop or start protein synthesis (translation).

coefficient of variation (CV) STANDARD DEVIATION SD divided by the arithmetic mean $\bar{x}$ and expressed as a percentage ($CV(\%) = SD / \bar{x} \cdot 100$); it permits the relative comparison of totally different sets of DATA ("apples vs. oranges"); see also CORRELATION COEFFICIENT.

coenzyme An organic compound that is necessary for the functioning of an enzyme. Coenzymes are smaller than the enzymes themselves and may be tightly or loosely attached to the enzyme protein molecule.

cohort Group of subjects with a common characteristic who are followed prospectively; see also IMMORTAL TIME BIAS.

cohort-event monitoring see PRESCRIPTION-EVENT MONITORING.

cohort study Investigates, e.g. a drug effect, prospectively, from exposure to outcome, in a group of patients without, or with appropriate control DATA (experimental c.s., observational c.s.); study in which subjects who presently have a certain condition and/or receive a particular treatment are followed over time and compared with another group who are not affected by the condition/have not this treatment (e.g. to follow the effect of smoking on health); in experimental c.s. (syn. randomized CONTROLLED CLINICAL TRIAL): cohorts of patients are prospectively and randomly allocated to treatment or control and effects (or ADVERSE EFFECTS, AE) are monitored; advantages: resistance to BIAS, great definitive POWER; disadvantages: time consuming, expensive,

brief study length identifies only short term AEs, size of study normally not large enough to permit identification of rare AEs; observational c.s.: relies on the follow-up of patients and controls; patients are non-randomly assigned a treatment, a comparable group (CONTROL) is selected and assigned to either no treatment or another treatment; both groups are then followed prospectively to determine the outcome; advantages: less expensive than experimental c.s., identifies new hazards even when they occur with a long latency, can estimate the RISK; disadvantages: appropriate control group may be difficult to define, follow-up is often incomplete, BIAS may be introduced by choice of patients for different treatment according to the characteristics of the individual drugs (e.g. evaluation of gastrointestinal AEs with non-steroidal anti-inflammatory drugs might be biased by allocation of patients with a pre-existing problem to drugs reputed to have the least effect on the GI tract); see also CASE-CONTROL STUDY, CROSS-SECTIONAL STUDY, FRAMINGHAM STUDY, IMMORTAL TIME BIAS, NESTED CASE-CONTROL STUDIES.

coinvestigator see INVESTIGATOR.

COLA design Stands for Change to Open Label design; subjects are included in a conventional randomized, controlled, blinded clinical trial as long as they agree to the treatment; primary endpoint is the time when the patient decides to withdraw and to follow an open label treatment; see also DESIGN,

co-marketing see CO-PROMOTION.

combining of lab data see POOLING OF LAB DATA.

commercial study (trial) see NON-COMMERCIAL CLINICAL TRIAL.

Committee for Proprietary Medicinal Products (CPMP) Committee of the EC formed by representatives of national registration authorities; members have to assess new applications for biotechnology and other novel medicines as well as to settle disputes between member states when they disagree as to whether a product may be licensed for use in their territory; for "high-technology" products the CPMP is the chosen but not mandatory approval route; see also CENTRALISED PROCEDURE, MULTISTATE PROCEDURE.

Committee on Safety of Medicines (CSM) Committee preceding the MEDICINES CONTROL AGENCY (MCA), now MHRA; and integrated in the Commission on Human Medicines; official body concerned with EFFICACY and SAFETY aspects (incl. licensing) of new MEDICINAL PRODUCTS in UK.

Committee for Veterinary Medicinal Products (CVMP) Official body within the EC similar to COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS.

Common Technical Document (CTD) Harmonised format of documentation to be submitted for marketing applications in the three ICH-regions; Module 1 contains the administrative and prescribing information documents specific to each regional regulatory agency; Module 2 contains the quality overall summary, the nonclinical overview and the clinical overview followed by nonclinical written summaries and the clinical summary. A one-page introduction of the pharmaceutical description should be provided; Module 3 provides the chemical-pharmaceutical and biological information for both chemically active substances and biological medicinal products; Module 4 and 5 contain the nonclinical and clinical study reports, respectively; each Module is preceded by a table of contents.

community based trials As part of an EXPEDITED DRUG DEVELOPMENT program simple, large, low-tech trials can be planned that collect less stringent data, generally on patients not eligible for standard trials.

community register (of medicinal products) The European Community maintains a public alphabetical list of medicinal products authorised in the EC (active – withdrawn/suspended – refused, with an index of brand names, active ingredient, ATC etc.; http://ec.europa.eu/health/documents/community-register.html/index_en.htm; access via ec.europa.eu/health/human-use/index_en.htm); see also FORMULARY, NATIONAL DRUG LIST.

Company Core Data Sheet (CCDS) ICH: "A document prepared by the MARKETING AUTHORISATION HOLDER containing, in addition to all relevant safety information, material relating to indications, dosing, pharmacology and other areas that are not necessarily safety related" (ICHe2c); syn. international prescribing information, "virtual SPC", core data sheet (CDS); central document that may be prepared by the marketing authorisation holder concerning a medicinal product covering material relating to safety, indications, dosing, pharmacology, and other information as a reference; synthesis of general information for prescribers on the correct use of a drug including risks; it is the reference document by which expected and unexpected adverse drug reactions are determined and is therefore always included in a drug safety update report; if there is an EC SPC this will take the place of the CCDS; the safety information contained within its central document (CCDS) would be referred to as "COMPANY CORE SAFETY INFORMATION" (CCSI); CCDS and CCSI are company-internal documents, the CCSI is used as "REFERENCE SAFETY INFORMATION"; see also DRUG SAFETY UPDATES, PATIENT INFORMATION LEAFLET (PIL), PERIODIC SAFETY UPDATE REPORT (PSUR), REFERENCE SAFETY INFORMATION, SUMMARY OF PRODUCT CHARACTERISTICS (SPC).

Company Core Safety Information (CCSI) ICH: "All relevant safety information contained in the (internal) COMPANY CORE DATA SHEET prepared by the MARKETING AUTHORISATION HOLDER (MAH) and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for EXPEDITED REPORTING" (expected/unexpected is used in association with official labelling); the CCSI is the minimum information that should be present in all documents relating to the safety of a product and part of the CCDS; it is also the common safety information that is included in all SPCs (common denominator) as authorized in Member States; the CCSI is appended to the PSUR including the date of last revision and highlighting any difference to the authorised text of the SPC; see also COMPANY CORE DATA SHEET, CORE SAFETY PROFILE, LISTED ADVERSE DRUG REACTION, SAFETY UPDATE REPORT, UNLISTED ADVERSE DRUG REACTION; for other types of documents see REFERENCE SAFETY INFORMATION.

comparative effectiveness research Research comparing clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose or treat diseases, disorders and other health conditions.

comparator product EC: "an investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial"; see also CONTROL, DESIGN, EVALUATION TECHNIQUE.

compassionate investigational new drug Also called TREATMENT IND; exemption from some of the FDA regulations to facilitate treatment of patients when alternate therapy is not available or is less effective.

compassionate use Also compassionate IND, sometimes mixed-up with single, NAMED PATIENT treatment, "pilot" application of a DRUG that has no marketing authorization but constitutes a significant therapeutic innovation for patients with a life threatening, chronically or seriously debilitating disease that cannot be treated satisfactorily by an authorized product; in the EC the medicinal product must be undergoing clinical trials or must be subject of an application for marketing authorization (Reg.726/2004); sometimes this is a first look to test a medical hypothesis, involving a very small number of, in most cases just a single patient; because it is so early in the development of the idea, there can be little specific evidentiary or other requirements governing such a use; there must be very careful observations and reporting on outcome made; see also EXPANDED-ACCESS PROGRAM, TREATMENT IND.

compendium of drugs see COMMUNITY REGISTER, NATIONAL DRUG LIST.

compensation for drug induced injury According to the EC guidelines on GOOD CLINICAL PRACTICE (III) "patients/healthy volunteers taking part in a clinical trial should be satisfactorily insured against any injury caused by the trial"; usual maximal sums are in the order of € 500,000.00 per patient or of € 10,000,000.00 per trial respectively; see also CLINICAL TRIAL COMPENSATION GUIDELINES, INDEMNIFICATION, INSURANCE, PRODUCT LIABILITY.

competition laws EC legislation prohibits agreements between undertakings designed to prevent or distort competition within the EC and which may affect trade between EC member states; the EC Commission can impose fines of up to 10 % of a group's annual worldwide turnover on each company involved in a breach; sums are in the order of DM 500,000.00 per patient or of DM 10,000,000.00 per trial respectively; competition rules apply also discounting and gifts; EC: "no gifts, pecuniary advantages, or benefits in kind may be supplied, offered, or promised to prescribers or suppliers, unless they are inexpensive and relevant to the practice of medicine or pharmacy"; see also CO-PROMOTION, JOINT MARKETING.

complementary medicine syn. alternative or non-conventional or traditional (e.g., Chinese) medicine often used along with conventional/standard or mainstream medicine resp., with treatments such as acupuncture, biofeedback, herbs, yoga etc.; see ALTERNATIVE MEDICINE, INTEGRATIVE MEDICINE.

complete case analysis Only those cases of a clinical trial are analysed where complete data sets are available; see also EXTENDER ANALYSIS, INTENT-TO-TREAT ANALYSIS, LAST VALUE CARRIED FORWARD, MULTIPLE IMPUTATION APPROACH.

complete response letter (CRL) Official letter of the FDA to a sponsor company, informing that a new drug application (NDA) or an abbreviated new drug application (ANDA) is not ready for approval; more than 25 % of the drugs approved in the US are delayed by CRLs with a median of 13 months; see also ACTION LETTER, NEW DRUG APPLICATION.

complete review letter The FDA Center for Biologics Evaluation and Research issues crl instead of "approvable" or "non-approvable" letters; this means that all data and information has been reviewed, but that it is not sufficient to support approval; deficiencies are described together with suggested remedial actions.

compliance Degree of cooperativeness and adherence of a patient to therapeutic advice or the dosage schedule resp.; depending on the burden of disease, about half to two-thirds of the patients (non-compliers) do not take medications as

prescribed (time, frequency, dose, duration, not filling a prescription/not taking the drug at all, inappropriate use with other drugs or alcohol, a.s.o.) which causes enormous burdens to health care systems by direct costs such as costs resulting from increased hospitalisation and interventions, but also indirect costs such as from lost productivity and premature deaths; compliance must be considered on a disease-by-disease basis and is also dependent on the age of patients with elderly being less compliant; a statement on compliance must be included in the final report of a clinical study as appropriate; increasing numbers of prescribed items are likely to cause decreasing compliance; methods for controlling c. are e.g. drug measurements in urine (e.g. colorimetric test on isoniazide) or blood, pill-counting, interviews and comments by the treating physician, electronic medication boxes that register each opening, a.s.o.; regardless of the degree of compliance all patients initially included in studies should be reported (INTENT-TO-TREAT principle); compliance can be increased with appropriate dose formulations (e.g. transdermal patches), low dosing frequency, pill calendars (or other forms of medication packaging), reminder devices (e.g. electronic pill boxes, counter caps, prescription label scratch-offs); see also DRUG HOLIDAYS.

component Refers to an intended constituent of a specific substance (e.g., dimethicone and silicon dioxide are components of simethicone; human insulin protamine and zinc are the components in human insulin isophane); see also CONSTITUENT, FORMULATION.

composite endpoint see COMPOSITE VARIABLE, GENIE SCORE, GLOBAL ASSESSMENT VARIABLE, VARIABLE.

composite variable Combines multiple measurements (e.g. severity of various symptoms) into a single new endpoint, so called composite variable, using a pre-defined algorithm; this avoids the problem of adjustment to the TYPE I ERROR due to multiple testing; in case rating scales are used, content validity, inter- and intra-rater reliability and responsiveness for detecting changes in the severity is particularly important; see also GENIE SCORE, GLOBAL ASSESSMENT VARIABLE, VARIABLE.

compulsory licensing (CL) syn. forced licensing; in some countries (e.g. Germany, Japan) health authorities can grant CL for a DRUG on a specific therapeutic area for public interest reasons or e.g. when a patented invention is not used by the originator during several years; use of the invention by a firm induces payment of a royalty to the patent owner.

computer assisted new drug application see CANDA.

computer assisted product licence application see CAPLA.

computer assisted product licensing application review see CAPLAR.

computerised system OECD: "A group of hardware components and associated software designed and assembled to perform a specific function or group of functions … Where computerised systems are used to capture, process, report or store raw data electronically, system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the person making those changes by use of timed and dated (electronic) signatures. Reasons for change should be given … Formal acceptance testing requires the conduct of tests following a pre-defined plan and retention of documented evidence of all testing procedures, test data, test results, a formal summary of testing and a record of formal acceptance"; see also CLOSED SYSTEMS, ELECTRONIC SIGNATURE, OPEN SYSTEMS.

concerned member state (CMS) see DECENTRALIZED PROCEDURE, ESSENTIALLY SIMILAR PRODUCTS, MUTUAL RECOGNITION PROCEDURE, RAPPORTEUR.

concertation procedure see CENTRALISED PROCEDURE.

concomitant event (CE) Event during treatment with a DRUG without anticipating relationship to the drug itself; see also ADVERSE REACTION.

concomitant medication Medication taken during treatment with a (test) DRUG; see also DRUG CHANNELLING.

condition (EU) In the context of orphan drugs, c. is defined as "any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)"; see also DISEASE, ILLNESS.

conditional approval (EU) syn. conditional marketing authorization, restricted marketing authorization under exceptional circumstances such as when particular aspects concerning efficacy or safety can only be identified/resolved when the product is marketed [Reg 1235/2010, Art.9(4)cc, Art.14(8)]; usually a time-limited approval based on SURROGATE ENDPOINTS, HISTORICAL CONTROLS or other type of limited information such as safety; further clinical studies (e.g. POST-MARKETING SURVEILLANCE, POST-AUTHORISATION SAFETY STUDY, POST-AUTHORISATION EFFICACY STUDY) may be a condition of marketing APPROVAL by health authorities; c.a. may be applied for by the sponsor if: (i) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; (ii) in the present state of scientific knowledge comprehensive information cannot be provided; (iii) it would be contrary to generally accepted principles of medical ethics to collect such information; independently, the

regulatory authority may request that the MARKETING AUTHORISATION HOLDER arranges for specific PHARMACOVIGILANCE data to be collected from targeted groups of patients for a period of 5 years following the initial placing on the market in the European Community (Vol.9A, but unlimited since Dir 2010/84, (9)); see also ACCELERATED APPROVAL PROGRAM, COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS, LEGAL STATUS, RESTRICTED MARKETING AUTHORISATION.

confidence interval Measure of the range which is likely to contain the true value of the parameter of interest; it indicates how large a true treatment difference may exist with a reasonable likelihood (usually 95 %); the c.i. reflects the variability or hetereogeneity of results and gives an indication of the degree of imprecision of the sample value as an estimate of the population value; the width of a c.i. is a measure of this imprecision and is the difference between the upper and lower confidence limits; the larger the SAMPLE SIZE, the narrower the width of the c.i. (all else being equal); c. limits for the results of a trial give the range of figures of the true response rate that are compatible or consistent resp. with the observed result for a given probability; the degree of consistency is determined by the confidence level (e.g. 95 %); confidence limits (CL) should always be reported in case of "negative" trials; 95 % CL = mean difference ± 1.96 ∞ STANDARD ERROR (difference); 90 % CL = mean difference ± 1.64 ∞ standard error (difference); see also ACCURACY, POINT ESTIMATION, RULE OF THREE, VARIABILITY.

confidence limits Upper and lower limit of the range of a CONFIDENCE INTERVAL.

confidential disclosure agreement (CDA) syn. confidentiality agreement, secrecy agreement; mutual written agreement between two parties concerning confidentiality of provided information; such documents are routinely used between pharmaceutical companies, companies and CONTRACT RESEARCH ORGANISATIONS, or investigators.

confidentiality Regarding trial subjects, EC (III): "maintenance of the privacy of trial SUBJECTS including their personal identity and all medical information; if DATA verification procedures demand INSPECTION of such details, this may only be done by a properly authorized person; identifiable personal details must always be kept in confidence; the trial subject's CONSENT to the use of records for data verification purposes should be obtained prior to the trial and assurance should be given that c. will be maintained"; – regarding material from the SPONSOR, EC: "maintenance of secrecy of confidential information from the sponsor in connection with the planning, execution, reviewing, AUDITING or evaluation of a CLINICAL TRIAL".

confidentiality agreement see CONFIDENTIAL DISCLOSURE AGREEMENT.

confidentiality of personal data According to the EC guidelines on GOOD CLINICAL PRACTICE (III) it ranks among the responsibilities of the INVESTIGATOR to "ensure that the confidentiality of all information about subjects is respected by all persons involved …" see also DATA PROTECTION ACT.

configuration see DESIGN.

conflict of interest Beginning 2013, companies producing medicinal products or devices must enter all payments to physicians exceeding US$ 10 in a publicly available database ("Patient Protection and Affordable Care Act").

confounder syn. confounding VARIABLE, nuisance v., interfering v.; variable that is related to both the outcome and exposure under study in such a way that it can create a false association or mask a real one, e.g. coronary artery DISEASE increases the risk of sudden death, older patients or patients with a longer duration of disease may have a worse prognosis, a non-experimental study with a β-blocker might demonstrate an excess of sudden deaths, or the LABELLING PHENOMENON; thus, even if the DRUG were efficacious (beneficial), it might appear harmful; in the absence of RANDOMIZATION, i.e. in a non-experimental study, to control for confounding v., one must be able to measure them; c. are not simply EFFECT MODIFIERS (which, in contrast, do not BIAS the overall estimate of exposure-outcome associations); see also LEARNING EFFECT, PLACEBO EFFECT, SIMPSON'S PARADOX.

consent see INFORMED CONSENT.

consent form Form used to obtain written or oral consent; in the latter case this form is not only signed and dated by the investigator but also the witness; these forms need to be approved by the responsible ethics committee; in some countries health authorities do not accept oral consent, e.g. Hungary; see also INFORMED CONSENT.

consistency of data Degree of association among items, plausibility; examples for c. checks: male patient who is pregnant, a patient's aging by more than 1 year over a 1 year period a.s.o.; see also MEASUREMENT PROPERTIES.

CONSORT Consolidated Standards of Reporting Trials; the CONSORT Statement is intended to improve the reporting of a randomized controlled trial (http://www.consort-statement.org/consort-statement/); see also PUBLICATION GUIDELINES, REPORT.

constituent Substance(s) present/mixed-up within a specified substance or substances that taken together form a product (can be e.g., degradation product(s), impurities, marker substance etc.); see also COMPONENT.

construct validity refers to the similarity in mechanisms underlying drug taking in the laboratory and drug taking in the natural ecology; see also VALIDITY.

consumer report information on an ADVERSE REACTION received directly from a patient/consumer (or other non-health care professionals); Dir 2010/84 encourages "patients, … healthcare professionals to report suspected adverse reactions to the national competent authority"; see also DIRECT PATIENT REPORTING, INDIVIDUAL CASE SAFETY REPORT, SIDE EFFECT.

consumption see MEDICAL CULTURE.

container closure system see PACKAGING SYSTEM.

contamination Undesired introduction of viable organisms such as bacteria or viruses; the term is sometimes used also for other IMPURITIES; see also BIOBURDEN.

contingency fees Legal fees contingent or conditional on the successful outcome of the plaintiff's case.

contingency table Tabulated DATA which are categorical, and mutually exclusive; entries into categories are actual numbers or counts; see also DATA MINING, SIGNAL.

continuation study Study with patients initially treated in a CONTROLLED CLINICAL TRIAL; the character of such studies is usually observational and a separate extension or follow-up protocol is used; see also COHORT STUDY.

continuous data syn. parametric data; data having an (theoretically) unlimited number of equally spaced DATA points, e.g. blood pressure values and most clinical laboratory measurements; suitable statistical tests are for two groups, unpaired samples the *t*-test, for two groups, paired samples Paired *t*-test, for multiple groups, unpaired samples F-test followed by pair-wise comparisons and for multiple groups, paired samples the modified F-test; see also DATA.

continuous reassessment method (CRM) Complex dose escalation model which uses all available data for calculating probability distribution for response vs. toxic dose; see also DOSE ESCALATION, FIBONACCI SEARCH SCHEME, MAXIMUM TOLERATED SYSTEMIC EXPOSURE (MTSE), PHARMACOKINETICALLY GUIDED DOSE ESCALATIONS (PGDE).

contra-label use see OFF-LABEL USE.

contract CRA Sometimes CLINICAL RESEARCH ASSOCIATES may be hired by a CONTRACT RESEARCH ORGANISATION or rarely by a pharmaceutical company only for the duration of a specific project or for a specific time.

contract house see CONTRACT RESEARCH ORGANISATION.

contract research organisation (CRO) Sometimes also called contract house, clinical research organisation (overall term: trial management organisation), third party service; EC (III): "scientific body (commercial or academic) to which a SPONSOR may transfer responsibility for some of its tasks or obligations"; FDA: "If a sponsor has transferred any obligations for the conduct of any clinical study to a CRO, a statement containing the name and address of the CRO, identification of the clinical study, and a listing of the obligations transferred may be submitted" (with a NEW DRUG APPLICATION); see also SITE MANAGEMENT ORGANISATION.

contraindication History or condition of a patient that indicates that a drug/treatment should not be used; absolute c.: treatment should not be used and under no circumstances; relative c.: when risks can be minimised e.g. by careful examination, monitoring a.s.o.

control Comparison with another treatment, either a concurrent treatment (internal or concurrent c.) or not (external c., often HISTORICAL C.); see also COMPARATOR PRODUCT, DESIGN, EVALUATION TECHNIQUE, EVIDENCE BASED MEDICINE, MATCHED PAIR, MÜNCH'S LAW, NEIGHBORHOOD CONTROL SUBJECTS.

controlled clinical trial (CCT) syn. experimental t., experimental COHORT STUDY; opp. non-experimental t., observational t.; any prospective CLINICAL TRIAL with one or more further groups of individuals (control) for direct comparison of outcome of a treatment; it is desirable to select at random the PATIENTS with the DISEASE process from the entire population with that disease (especially if extrapolations to the entire population are to be made) as well as to allocate the patients to groups at random; before RANDOMIZATION patients may be STRATIFIED into different categories of RISK or prognosis; assessment of treatment should ideally be double-BLIND; if a control group is compared with more than one active treatment the control needs to be larger in order to gain maximum POWER for a given SAMPLE SIZE (as a rule of thumb the number of subjects for the control group is multiplied by the square root of the number of active treatments); see also DESIGN; NON-COMPARATIVE STUDY.

controlled drug Drugs known for inducing dependence such as e.g. morphine, methadone, barbiturates, codeine, amphetamines a.s.o.; usually special arrangements apply to the prescribing of such drugs; in some countries, e.g. UK, only physicians holding a special license may be allowed to prescribe a c.d.; see also DESIGNER DRUG, GENERAL SALE LIST MEDICINE, GRAS-LIST, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE.

controlled release form (CR) syn. controlled delivery; dosage form (usually oral) designed to release drug(s) slowly in the gastrointestinal tract, ideally irrespective of the concentration according to a zero order KINETIC; such formulations frequently use e.g., polymer coatings, polymer/drug-extrudate preparations (usually drug crystals embedded in a polymer matrix, HOT-MELT EXTRUSION), hydrophilic matrices (hydroxypropyl methylcellulose), wax matrices, polyethylene oxide, or osmotic pump devices; see COATING, DELAYED RELEASE FORM, DISSOLUTION TEST, FORMULATION, MODIFIED RELEASE, TRANSDERMAL PATCH.

conventional medicine syn. "school medicine", opposite to ALTERNATIVE MEDICINE.

cooperativeness see COMPLIANCE.

co-payment Patients pay a fixed sum or a percentage for pharmaceuticals prescribed by their doctor or for hospital stays, or for other health services, the rest is paid by the health insurers; see NEGATIVE LIST, POSITIVE LIST, REIMBURSEMENT SYSTEMS BLACK LIST.

co-primary endpoints Intersection unit principle; see PRIMARY ENDPOINT.

co-promotion The same DRUG is promoted by two or more companies under a single TRADEMARK; in case of "co-marketing", the same medicinal product is promoted by two or more companies but under different brand names; c.-p. achieves greater visibility in the marketplace and makes entry of new competitive drugs more difficult; see also COMPETITION LAW, JOINT-MARKETING.

core protocol Clinical trial protocol defining basic and important issues for a particular trial.

core safety profile (CSP) simplified and harmonised document provided by the originator (innovator only!) of a medicinal product that contains all safety information in the SPC (SmPC)-format; it includes common information from sections 4.3 to 4.9 present in all SPCs within the EU and any relevant safety information from 4.2 and is intended to help the assessment of differences in national SPCs; updates are with the next PSUR; see COMPANY CORE DATA SHEET, COMPANY CORE SAFETY INFORMATION.

correction see CORRECTIVE AND PREVENTIVE ACTION.

correction log see DATA RESOLUTION FORM.

correction of errors In a CASE RECORD FORM corrections should be made by the investigator as follows: (1) draw a single line through the error so that the original entry remains visible; (2) enter new value alongside (preferably with a black ball point pen); (3) initial (initials of the investigator); (4) date; (5) give reasons for correction.

corrective and preventive actions (CAPA) During inspections, inspectors expect to see a program how deviations from quality are handled by a company; corrective action is defined by the FDA as "action taken to eliminate the causes of an existing non-conformity defect or other undesirable situation in order to prevent recurrence"; in contrast "correction" refers to repair of an existing non-conformity; see also INSPECTION, QUALITY CONTROL.

correlational study Looks for a (linear) correlation of a specific outcome with a risk factor (exposure) in a whole population (e.g., lung cancer – number of cigarettes/day; breast cancer – per capita intake of saturated fat); such designs can generate hypotheses but may not be conclusive on a more individual level or a level of less aggregated data resp. (risk of ECOLOGICAL FALLACY); see also CROSS-SECTIONAL STUDY.

correlation coefficient syn. Pearson correlation coefficient; descriptive statistic; indicates relationship (extent of linear correlation) between two continuous VARIABLES; the better comparable the DATA resulting from two different methods are (i.e. the closer the correlation is) the more the r value approaches the value 1, whereby 0 represents no correlation, –1 a perfect inverse correlation (negatively sloping line) and +1 a perfect positive correlation; as a rule of thumb data should always be visualized as scatter-plot before reporting linear correlation; the square of r signifies the proportion of the variation explained (thus, a r of 0.2 means that the supposed relationship only explains 4 % of the variation); r is defined mathematically as:

$$r = \frac{\sum (x_i - \bar{x})\,(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

see also COEFFICIENT OF VARIATION, LINEAR REGRESSION.

cosmetic FDA: "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance; articles intended for use as component of any such articles, except that such term shall not include soap"; see also EMOLLIENT, NANOPARTICLES.

costs see ADVERSE REACTION, CLINICAL TRIAL, DRUG CONSUMPTION, EUROPEAN MEDICINES AGENCY, HEALTH CARE COSTS, HEALTH CARE SERVICES, MARKETING AUTHORISATION, PHARMACEUTICAL MARKET, PHARMACOVIGILANCE, PRICE REGULATORY SCHEME, PRESCRIPTION, REIMBURSEMENT, RESEARCH AND DEVELOPMENT.

COSTART see CODE.

cost/benefit analysis (CBA) Sometimes used as overall term for ECONOMIC ANALYSES such as COST/EFFECTIVENESS A., COST/UTILITY A., and QUALITY OF LIFE STUDIES; in a narrower sense the term CBA is confined to studies where both the resources used and the benefit a treatment yields can be expressed in monetary terms (e.g. a specific treatment avoids later costs of surgery or hospitalisation, money saved/lost when medications exert beneficial/adverse health effects); CBAs are often used to justify the price of a product. The result of a CBA can be a "major added benefit", "significant added benefit", "unquantifiable additional benefit" or "no added benefit"; a treatment is most cost-beneficial if the economic return exceeds the treatment costs (highest net benefit) or if it has a higher ratio of benefits to costs (B/C); economic analyses require specification of the treated populations and treatment procedures; depend therefore on the social context, on the indications for which the drug is prescribed, on the characteristics of the treated population and on the dosage schedules; for the manufacturer they may be useful to demonstrate therapeutic advantages also of marginally innovative products and to support price negotiations or rationalise reimbursement decisions; economic analyses are rarely required by health authorities, e.g. in Australia, Canada, and Germany (the so called "Arzneimittelmarkt-Neuordnungsgesetz"/ AMNOG since January 2011, but not by the FDA); they may however be required for REIMBURSEMENT by health insurance systems; see also DELTA VALUE, DISEASE MANAGEMENT.

cost/consequence analysis (CCA) Lists advantages and disadvantages, without giving a bottom line total, leaving the adding up and weighting of the data to the decision maker.

cost/effectiveness analysis (CEA) Measures effectiveness of a treatment in natural, not monetary units, e.g. days off work, years of life gained; shows the least cost per outcome measure gained, comparing the costs of achieving the desired outcome (effect) by a variety of treatment methods; CEA shows therefore how to spend resources most effectively given a particular desired objective; (e.g. cost per pound lost for measuring c./e. of weight loss programs, cost of means of avoiding an infant death per year of life gained); most appropriate for comparison of treatments not producing an equivalent likelihood of clinical outcome; cost/effectiveness data are increasingly used to facilitate regulatory approval, justify pricing and influence REIMBURSEMENT; Australia and Canada request economic data to support product application and reimbursement listing since 1993, in France CEA and QUALITY OF LIFE data are explicit criteria for determining prices and reimbursement; it is likely that other European authorities will follow; see also ECONOMIC ANALYSIS, EFFECTIVENESS.

cost/minimisation analysis (CMA) Compares net costs of treatments which have identical medical outcomes (patient outcomes are all the same); not to be

confounded with a cost-of-illness study, where total costs (direct and indirect) attributable to a given illness are calculated.

cost/utility analysis (CUA) Synthesizes simultaneously multiple outcomes (e.g. on both MORBIDITY and MORTALITY, pain and physical function, but also quality) into a single measure; the basis for this type of analysis is that each outcome is weighted by a person's preference ("utility") for experiencing the outcome; CUA relates therefore the costs of different procedures to the increased utility which they produce e.g. in terms of QUALITY-ADJUSTED LIFE-YEARS (QUALY) gained; the treatment with the lowest costs per QALY is to be preferred; see also QUALITY OF LIFE, UTILITY MEASUREMENT.

Council for International Organisation of Medical Sciences (CIOMS) International, non-governmental, non-profit organization (http://www.cioms.ch/); set up under the auspices of the WHO and UNESCO; acts as sounding board for capturing and disseminating informed opinion on new developments in biology and medicine, but explores also their social ethical, moral, administrative and legal implications; well known is also the so called CIOMS I-FORM for reporting suspect ADVERSE REACTIONS to the WHO centre in Uppsala and which is accepted as report form by a number of health authorities, e.g. in Germany, France, Italy, Ireland, The Netherlands and UK; this form is almost identical with the form FDA 1639 and accepted by the US authority.

counterfeit medicine a medicine that is deliberately and fraudulently mislabelled with respect to identity and/or content and/or source; c.m. may make between 1 and 30 % of the market and represent a safety concern; in 2010, customs in the EC seized 103 million products suspected of being counterfeit, 68 % of them originated from China and 28 % from India; see also FALSIFIED MEDICINAL PRODUCT.

country code see also ISO COUNTRY CODES.

covariate VARIABLE assumed to be related to the treatment RESPONSE.

creatinine clearance (CCr) A widely accepted formula for calculating the CCr from the serum creatinine Cr is that put forth by Cockcroft and Gault (Nephron 1976, 16: 31–41): male CCr = [body weight (kg) × (140 – age)] divided by [72 × Cr (mg/100 ml)]; female CCr = 0.85 × above; see also CLEARANCE, GLOMERULAR FILTRATION RATE.

CRF correction log see DATA RESOLUTION FORM.

critical path method (CPM) PROJECT MANAGEMENT TECHNIQUE which calculates total duration of a project based on individual task durations and dependencies, and identifies which tasks are time-critical.

critical term list WHO-originating list of about 50 selected ADVERSE REACTIONS which are considered indicative of more serious clinical problems; see WHO-ADVERSE REACTION TERMINOLOGY.

cross contamination EC (IV): "contamination of a starting material of a product with another material or product"; see also CLEAN AREA, CONTAMINATION.

crossing over Exchange of genes between two paired chromosomes.

crossover Two period (two-way), three period (three-way), four period or multiperiod comparison (within- or between-SUBJECT); each subject receives two treatments one after the other (or simultaneously e.g. left vs right for topical treatments), the order of treatment being decided randomly; although this is a common design to demonstrate bioequivalence, clinical studies with such a design are infrequent (only for agents with prompt onset and rapid offset of effects and diseases with a stable course); see DESIGN, HEATON-WARD EFFECT.

cross-sectional study Provides a "snapshot" of the frequency and characteristics of a disease in a population at a particular single point in time; basically identical to CASE-CONTROL STUDY except that the VARIABLE assumed to be the cause of an event (or DISEASE) is measured at the same time as the assignment of the patient to the event/disease category. In a cross-sectional survey, a specific group is looked at to see if a substance or activity, say smoking, is related to the health effect being investigated – for example, lung cancer. If a significantly greater number of smokers already have lung cancer than those who don't smoke, this would support the hypothesis that lung cancer is caused by smoking; c.s.s. usually measure PREVALENT outcomes, DROPOUTS, fatal cases, migrants a.s.o. are not counted (example: assumption of a relationship between deep vein thrombosis and pills for birth control; if a true relationship exists the patient was taking the pill at the time when the thrombosis occurred; a history of pill-taking in the past would be much less conclusive); best suited for chronic, nonfatal conditions; disadvantages: frequently c.s.s. are unable to distinguish cause from EFFECT possibility for selection BIAS; see also ASSOCIATION STUDY, CASE-CONTROL STUDY, COHORT STUDY, CORRELATIONAL STUDY, ODDS RATIO, PHARMACOVIGILANCE.

CTX-scheme see CLINICAL TRIAL EXEMPTION.

cultural background Term is used by FDA to encompass such socio-economic characteristics as age, ethnic origin and economic status.

cumulative incidence Number of patients diagnosed with the disease of interest in a fixed (initial) population observed for a specified time (proportion, not a rate); see also INCIDENCE RATE.

cure Elimination of an abnormal condition, in the best case also of the cause of this condition, as a result of a specific treatment (e.g. by a physician); see also HEALING.

CUSUM plot From "cumulative sum"; a method which is employed for examining if there is a drift in the results in long term trials or laboratory results; for each measurement during the trial the difference is calculated between this figure and the initial mean result; the cumulative sum is calculated during the course and plotted against the time; see also BIAS, SEQUENCE EFFECT.

cut-off date see DATE LOCK-POINT.

cytochroms P450 (CYP P450) A complex mixture of enzymes with metabolic, biosynthetic and bio-modulating functions; clinically most relevant are CYP1A2, CYP3A, CYP2C9, CYP2C19, CYP2D6; many of them can exist in an number of ALLELES (e.g., more than 30 alleles known for CYP2C9); as such alleles differ in their enzymatic activity/metabolic capacity this results e.g., in genotypes that are "extensive" or "poor metabolisers"; CYP3A is responsible for about 50 % of the drug oxidations, CYP2D6 for another 30 % and CYP2C9 for about 15 %; about 5–10 % of all Caucasians possess no active CYP2D6 enzyme, up to 6 % are deficient for CYP2C19; drugs or food components cannot only be substrates for these enzymes but are also able to induce or inhibit them (e.g., grapefruit juice inhibits intestinal CYP3A and other enzymes); CYP P450 enzymes are thus responsible for many drug-drug or drug-food interactions; see also GENETIC VARIANCE, GENOTYPE, INTERACTION OF DRUGS, METABOLISM, www.im.ki.se/CYPAlleles.

cytotoxic Able to cause cell death; a cytotoxic substance usually is more subtle in its action than is a biocide.

D

DAMOS (Drug Application Methodology with Optical Storage) Standardised interface between pharmaceutical companies and regulatory authorities for transferring information, e.g. documents for registration.

data Types of data (VARIABLES) are: either continuous (quantitative, dimensional, parametric, interval) d.: have an almost unlimited number of equally spaced data points, expressed in integers, decimals or fractions e.g. body temperature, blood pressure, pulse rates, age, number of events, and most clinical laboratory measurements; suitable statistical tests for normally distributed continuous d. are t-tests and analysis of variance; or categorical (qualitative, discrete, proportional) d.: entity measured fits either into one of two categories (=dichotomous (binary-, paired) d.) e.g. yes/no, female/male, dead/alive, worsened/improved, percentage cured or dead a.s.o. (suitable is e.g. chi-square test; when examining the change in a proportion over time in the same subjects (within group comparison), then an analysis suitable for paired d. could be performed, e.g. Mc Nemar's test) or in more than two categories (=polychotomous d.) e.g. taste, race, colour, study centre location (=nominal d. with no ordered relationship), or with an ordered relationship to one another and which can be ranked into three or more categories (=ORDINAL d.) e.g. pain- or ADVERSE EVENT scales (mild, moderate, severe), psychiatric SCALES (often pseudocontinuous i.e. the difference between +1 and +2 is not the same as between +3 and +4), complete, partial, no RESPONSE or progression, a.s.o.; include also many of the subjective measurements such as VISUAL ANALOGUE SCALES; "hard" (opposite soft) data=d. which do not depend on observer ERRORS and are precisely measured; see also DISTRIBUTION, ELECTRONIC DATA, OUTLIERS, PRIMARY ENDPOINT, RAW D.

data analyst see DATA MANAGER.

data archiving see ARCHIVING.

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data audit trail see DATA TRAIL.

data base see RELATIONAL DATA BASE; see also CLINICAL TRIAL DATA BASE, EUDRACT.

data capture document Document for recording data; see CASE RECORD FORM, SOURCE DATA.

data clarification form (DCF) see DATA RESOLUTION FORM.

data coding see CODE.

data collection form (DCF) see CASE RECORD FORM.

data dictionary Electronic or written information for each type of DATA or element containing the name, definition, size, type, (normal) range, where and how it is used, its relationship to other data a.s.o.; the d.d. describes the DATA BASE and ensures consistency across individual databases; such a repository does, however, not contain the actual data itself.

data dredging Multiple, exhaustive analysis of data until the (wanted) result has been found; see also BONFERRONI CORRECTION, MULTIPLE COMPARISONS.

data edit form see DATA RESOLUTION FORM.

data editing syn. data monitoring; checking of each recorded answer to every question of a questionnaire to ascertain whether the collected data are valid with respect to range (OUTLIERS), format, content, completeness, ACCURACY, legibility, plausibility (logical inconsistencies as e.g. male sex and gravidity), and CONSISTENCY (e.g. a patient suffering from diabetes at the time of recruitment must also have a diabetes at the end of the study), as well as the process of transformation of these data; e.g. into new units, which make them comparable with the same type of data of another trial; d.e. can be made at any step after receipt of the CASE RECORD FORM (before or after DATA ENTRY); part of such verification processes can be made by special computer programs; to detect doubtful data, descriptive statistics are useful, especially on important variables; see also POOLING OF LAB DATA.

data entry Transfer of observations, usually from a CASE RECORD FORM (CRF) or another written document to an electronic medium or direct entry into an electronic CRF (eCRF); this is achieved either by single d.e., normally checked by proofreading (at least for the primary VARIABLES), or by double d.e. (enters made by one operator are checked against that of a second in order to reduce KEY-PUNCH ERRORS to a minimum, whereby most often operators will be kept "blind"); in interactive d.e., range and cross-checks on the figures entered are executed immediately, which has major advantages: the investigator is warned

of ERRORS immediately, time spent later on data checking is reduced, retrieval of the patient's file at a later date to answer inconsistencies is avoided, data integrity is assured; at the begin of the d.e. process a data entry screen, matching the CRF as close as possible, has to be prepared; other possibilities of d.e. are continuous, ongoing d.e. (opposite: batch input), automated reading (with optical mark or optical character recognition, and facsimile transmission); see also REMOTE DATA ENTRY, WEB-BASED DATA ENTRY.

data handling manual Manual describing what must be done with data of a clinical trial, beginning when they are received by the biometric department till closure of the data base; see also DATA CODING, D. EDITING, D. ENTRY, D. LOCKPOINT, D. MANAGER, D. RESOLUTION, D. TRAIL, D. VALIDATION.

data lock-point (DLP) syn. data cut-off date; ICH: "The date designated as the cut-off date for data to be included in a PERIODIC SAFETY UPDATE REPORT. which is based on the INTERNATIONAL BIRTH DATE (or HARMONISED BIRTH DATE) and should be in six-monthly increments"; date at which a data base is "frozen" or "closed" in order to follow development of stored information, e.g. for PSURs and their resp. statistical analysis, or every 6 months for the first 2 years subsequently to the date of the first approval by the first regulatory authority for a particular drug; see also PERIODIC SAFETY UPDATE REPORT; the DLP is 2 months earlier than the date of the updated PSUR; other documents that need regular review such as the INVESTIGATOR'S BROCHURE do not have a defined DLP.

data manager Responsible person for the DATA and administrative activities of a clinical research process from the very beginning till the generation of the final report; she/he designs trial forms, ensures that randomization and data collection are conducted according to the PROTOCOL, ensures correct DATA ENTRY, logic checks (e.g. blood pressures, heart rates, etc. checked for certain acceptable values) and editing, as well as documentation in a data master file within a data centre, ready for use by the statistician; the d.m. is also responsible for data base creation, its structure, and maintenance; together with the MONITOR she/he is responsible for resolving data QUERIES; a data analyst may assist the d.m.

data mining syn. "knowledge detection"; Process of sorting through large amounts of data and picking out relevant information; statistical and logical (disproportionality) analysis of large sets of data, looking for patterns that can aid (e.g. safety) decision making (useful: visual exploration of relationships with e.g., SHIFT TABLE/TRANSITION MATRIX, histograms, distribution curves, etc.); d.m. for adverse reactions relies on medical dictionaries for adverse events; however, results can be affected by coding redundancies of such hypergranular dictionaries as the MedDRA where a single high level term comprises preferred

terms which present very different medical concepts or conditions which differ greatly in their clinical importance (e.g., PTs related to liver injury: 'Jaundice', 'hepatitis', 'hepatotoxicity', 'hepatic failure', 'hepatic necrosis', 'acute hepatic failure'); this leads to "signal fragmentation"; used for SIGNAL DETECTION in PHARMACOVIGILANCE; see also DISPROPORTIONALITY ASSESSMENT, MEDICAL DICTIONARY FOR DRUG REGULATORY ACTIVITY.

data monitoring see DATA EDITING.

data monitoring committee (DMC) see DATA SAFETY MONITORING BOARD.

data protection act In most countries the storage of personal data in electronically processed form is regulated by law; companies storing information must be registered in a national Data Registrar. see also CONFIDENTIALITY.

data quality In order to be acceptable, data must be attributable, legible, contemporaneous, original and accurate (ALCOA). These quality and integrity criteria are applicable to all data, whether they are collected on paper or recorded electronically; see also ELECTRONIC DATA, RAW DATA, SOURCE DATA.

data resolution form (DRF) syn. CRF correction log, data clarification form, data edit form, notice-of-change form, query log, query resolution form; form used by MONITORS or CLINICAL RESEARCH ASSOCIATES to collect missing or to correct illegible, wrong or implausible entries in CASE RECORD FORM (CRF); once collected, CRF never go back to the investigator; see DATA MANAGER.

data and safety monitoring board (DSMB) syn. Data Monitoring Committee (DMC); group of independent researchers who review data from a blinded, controlled clinical trial; they may decide on its' continuation or stop if safety and/or benefit/risks concerns arise; see also SAFETY ANALYSIS, STEERING COMMITTEE.

data sheet see SUMMARY OF PRODUCT CHARACTERISTICS.

data trail syn. AUDIT trail; integrity of the documentation record which allows a MONITOR, auditor or inspector to follow the process of events from patient record to NEW DRUG APPLICATION and to confirm that the correct procedures were followed; record of all changes made to DATA after the data were originally entered.

data transfer Data can be transferred to the data management centre either by hard-copy CRFs, faxed copies of CRFs, diskettes or tapes, or electronic data files via modem; see also CASE RECORD FORM (CRF).

data validation Process to ensure that data in the data base or final report accurately reflect data in the case record forms.

dead line Ultimate date till e.g. a CLINICAL TRIAL has to be finished.

Dear Doctor letter syn. 'Dear Health-care Professional' letter, 'Dear Prescriber' letter; see DIRECT HEALTH CARE PROFESSIONAL COMMUNICATION, RISK MANAGEMENT SYSTEM, SAFETY COMMUNICATION.

death rate see MORTALITY RATE.

debriefing meeting syn. closing meeting, exit debriefing; see EXIT INTERVIEW, FDA 483 FORM.

decentralised procedure – multistate procedure, applicable in cases where an authorisation does not yet exist in any of the Member States (MS); identical dossiers will be submitted in all MS where a marketing authorisation is sought (concerned MS); the reference MS, selected by the applicant, will prepare draft assessment documents within 120 days and send them to the concerned MS. They, in turn, will either approve the assessment or the application will continue into arbitration procedures; see also CENTRALISED PROCEDURE, MUTUAL RECOGNITION PROCEDURE.

dechallenge Improvement of an ADVERSE REACTION after stopping the DRUG; see also CAUSALITY, RECHALLENGE.

decision analysis syn. benefit-risk a.; systematic strategy by which the ramifications of each possible decision are compared for all relevant outcomes; the most common approach is in general to construct a decision tree, estimate the probabilities of its branches and assign UTILITIES to its possible final outcomes; other strategies are e.g. the "minmax" strategy (decision with the minimum probability of the maximum loss, opposite: "gambling" approach – decision with the maximum possibility of the most favourable outcome) or a more scientific approach where decisions are made according to results of investigations in the past which show "significant" differences in favour of one decision.

decision tree see DECISION ANALYSIS.

Declaration of Helsinki Comprises recommendations of the World Medical Assembly, guiding physicians in biomedical research involving human SUBJECTS; adopted in Helsinki, Finland (1964), amended in Tokyo, Japan (1975), Venice, Italy (1983), Hong Kong (1989), at the 48th General Assembly, Somerset West, Rep. of South Africa, Oct. 1996, at the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, and at the 59th WMA General Assembly, Seoul, October 2008, 7th revision (http://www.wma.net/en/30publications/10policies/b3/); see also NUREMBERG CODE.

defect see PRODUCT DEFECT, PRODUCT RECALL.

defined daily dose (DDD) Assumed average dose per day for a drug used in its main indication in adults; basis for cost comparison of medicinal products for REIMBURSEMENT; see http://www.whocc.no/atc_ddd_index/ (search options enable to find DDDs for substances and/or ATC codes, the index is maintained by the WHO); see also ACCEPTABLE DAILY INTAKE, ANATOMICAL THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM, OVERDOSE.

degradation products Undesirable products that result from the synthesis (e.g., solvents, intermediates), storage/aging (environmental factors) or the formulation (e.g., excipients); see also CONTAMINATION, IMPURITY, STABILITY TESTS.

delayed release Opposite: instant delivery/immediate release; modified release product in which the release of the active substance is delayed for a finite "lag time", after which release is unhindered (e.g., enteric coated or gastro-resistant oral tablets or capsules which remain intact in the stomach and only disintegrate in the higher pH of the small intestine); delayed release results in a longer T_{max} but with T_{max} and elimination half life unchanged (European Pharmacopoeia, EudraLex 3AQ19a: Quality of prolonged release oral solid dosage forms, Nov. 1992); see also CONTROLLED RELEASE, DISSOLUTION TEST, PROLONGED RELEASE.

delta value syn. minimum relevant difference, smallest clinically meaningful difference; size of a clinically or therapeutically meaningful difference (e.g. improvement in outcome, tolerance, costs) that a trial is designed to detect; in experimental trials delta should be set to define an improvement that is great enough that most people would select the new treatment despite its potential unknown hazards; see also ALTERNATIVE HYPOTHESIS, BETA ERROR, SAMPLE SIZE ESTIMATION.

demographic data DATA describing basic characteristics of subjects in a clinical trial, e.g. age, sex distribution, ethnic origin, length of current disease, number of subjects treated de novo a.s.o.; see also BASELINE VARIABLES.

dependency (physical) characterized by withdrawal symptoms (abstinence syndrome) upon cessation of the drug; see WITHDRAWAL (substance).

depletion bias see BIAS.

depth of product recall see PRODUCT RECALL.

derived variable Variable created from other variables; example: body mass index (BMI) which is calculated using height and weight of a subject; see also META-DATA.

descriptive statistics Presentation of results by their median, arithmetric mean, standard deviation, mode, distribution of data with min. max. values a.s.o.; see also INFERENCE STATISTICS.

D

design Cross-over d. (opp. parallel) = two period or multi-period comparison (within- or between-SUBJECT); each subject receives two treatments one after the other (or simultaneously e.g. left vs right for topical treatments), the order of treatment being decided randomly; this d. is appropriate when the DISEASE process or subject is relatively stable (e.g. BIOEQUIVALENCE studies in healthy volunteers, M. Parkinson, myasthenia a.s.o.), when treatments are not curative, when periods of treatment are short, when there is no interaction or ORDER EFFECT and when the number of DROPOUTS and WITHDRAWALS can be kept low; within-subject studies allow in general a more precise comparison of treatments and require an about 2,6 times smaller number of subjects than between-subject studies; a WASH-OUT PERIOD is usually essential between treatments to eliminate drug or drug-effect CARRY-OVER; special types of cross-over d. are LATIN SQUARE d., and GRAECO-LATIN SQUARE d.; a FACTORIAL d. can be planned either as cross-over or as parallel d. and answers two questions at the "price" of one; parallel d. = simultaneous group-comparison, e.g. two group parallel d.; in this simple, standard d. subjects are randomised to either the test treatment (experimental group) or to a control (placebo, no treatment, active treatment or positive control, dose comparison); positive results reported in open studies without control (i.e. without further parallel group(s) for direct comparison) should be confirmed by controlled clinical trials later on; fixed sample size (closed) d. = the number of subjects is defined according to a specified difference between treatments; opposite: open d. = sample size is allowed to increase indefinitely; if the control group has not been treated simultaneously but somewhere in the past, this is called a HISTORICAL COMPARISON; fixed SAMPLE SIZE VARIANCE trials, rechallenge trial: the hypothesis is that a patient will, if repeatedly exposed, experience once more a beneficial or, more frequently, an adverse reaction to a specific medication; most often this is done on a single patient who serves as his own control (SINGLE CASE EXPERIMENT); randomized withdrawal trial = patients on a specific treatment due to a specific DISEASE (e.g. chronic treatment with anticonvulsives or digitalis) are randomly assigned to either a CONTROL (e.g. PLACEBO) or an experimental group, "early escape" (treatment fails or subject does not tolerate treatment) can be an endpoint (caveat: efficacy and tolerance may be better than expected because of enrichment of "responders"); natural endpoints are the (predefined) worsening using standard time-to-occurrence statistical tests or a comparison of proportion of outcomes; see also ASSOCIATION STUDY = investigates associations between one VARIABLE and another (e.g. cause-effect rather than size and significance of differences) in groups treated with one intervention versus another; see also ADAPTIVE DESIGN, CASE SERIES, CLUSTER RANDOMISED CONTROLLED TRIAL, COLA DESIGN, CROSS-SECTIONAL STUDY, GEHAN'S DESIGN, LARGE SIMPLE TRIAL DESIGN, NON-COMPARATIVE STUDY, OBSERVATIONAL STUDY, ONE SAMPLE MULTIPLE TESTING DESIGN, RANDOMIZED CONSENT D., REPEATED MEASURES D., SEQUENTIAL D., STEADY STATE STUDY.

designer drug Drugs ("legal highs") that are analogues of controlled substances with modifications of an existing structure; dd replace the existing drug when e.g., the latter is banned, circumventing legal issues; most are distributed over the internet; see also CONTROLLED DRUG.

detailed description of the pharmacovigilance system (DDPS) was introduced in September 2008 ("Volume 9A"); a DDPS is no longer requested to be joined to applications for marketing authorizations; it has been superseded in December 2010 by the PHARMACOVIGILANCE (SYSTEM) MASTER FILE (PSMF).

development Relates often to the improvement of a product; in the pharmaceutical industry the d. stage can be seen as the clinical part of the research process; in other industries distinction between d. and research can be problematic and may implicate financial consequences (tax authorities may refuse tax relief on expenditures which they define as development, i.e. improvement of an already marketed product, rather than research); see RESEARCH AND DEVELOPMENT.

development international birth date (DIBD) "Date of first approval (or authorisation) for conducting an interventional clinical trial in any country" (ICH E2F); see also BIRTH DATE, INTERNATIONAL BIRTH DATE.

development safety update report (DSUR) replaces the IND Annual Report (US) and Annual Safety Report (EC), implemented in September 2011; annual report that provides safety information of an investigational drug from all ongoing clinical trials that the sponsor is conducting or has completed during the review period; start of the periodicity is the DEVELOPMENT INTERNATIONAL BIRTH DATE; the covered period of a DSUR is 1 year and is to be submitted until the last visit of the last patient in a clinical trial in the member state concerned; a DSUR is also needed in phase IV; the main objective of a DSUR is to (1) summarise the current understanding and management of identified and potential risks; (2) describe new safety issues that could have an impact on the protection of clinical trial subjects; (3) examine whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the product's safety; and (4) provide an update on the status of the clinical investigation/development programme (ICH E2F); reference safety information for a DSUR is the INVESTIGATOR'S BROCHURE or the SUMMARY OF PRODUCTS CHARACTERISTICS (PACKAGE INSERT in Japan and USA); the DSUR overlaps with the INVESTIGATOR'S BROCHURE/INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (before authorization) and the PSUR (post-authorisation); any scientific advice the sponsor has received by a competent authority has to be included in the DSUR; if development of a medicinal product continues after marketing authorization the respective company must maintain two safety update reports despite of considerable overlapping; see also ANNUAL PROGRESS

REPORT, ANNUAL SAFETY UPDATE REPORT, COMPANY CORE SAFETY INFORMATION, DATA LOCK POINT, PERIODIC SAFETY UPDATE REPORT, REFERENCE SAFETY INFORMATION, SUSAR.

deviation log List of deviations from the clinical trial PROTOCOL observed by the MONITOR or STUDY NUSE; not an "ESSENTIAL DOCUMENT"; see also MONITORING PLAN.

device FDA: "instrument, apparatus, machine, implement, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is (1) recognized in the Official National Formulary, or the US Pharmacopoeia, (2) intended for use in the diagnosis, treatment or prevention of DISEASE, (3) intended to affect the structure or any function of the body of man or animals and which does not achieve its purposes through chemical action within the body and which is not dependent upon being metabolized"; in the US, devices are placed in three classes, all of which are subject to regulatory aspects such as premarket notification, registration and listing, prohibitions against adulteration and MISBRANDING, and rules for GOOD MANUFACTURING PRACTICES; in addition, class II d. also need performance standards, and class III d. need premarket approval; examples for class I d.: needles for injections; examples for class II d.: electrocardiographs, powered aspirators to remove blood, loose bone chips a.s.o. during surgery, haemodialysers; examples for class III d.: heart valves, inflatable penile implant, electrohydrolic lithotripter; see also BIONICS, BIOPROSTHESIS, DEVICE MASTER RECORD, EC DECLARATION OF CONFORMITY, MEDICAL DEVICE.

device master record (DMR) FDA: "compilation of records containing the design, formulation, specifications, complete manufacturing procedures, quality assurance requirements and labelling of a finished device"; overall documentation required to manufacture devices (e.g. general documents such as STANDARD OPERATING PROCEDURES, but also documents for procurement, processing, labelling, packaging, tests or INSPECTIONS); an individual must be designated to prepare, date, sign, and approve the DMRs and authorize changes; according to the FDA, all records pertaining to a device must be retained for at least 2 years from the date of release for commercial distribution; see also DEVICE, MEDICAL DEVICE.

diagnosis see CODE, LABELLING PHENOMENON, STAGING.

diagnostic A product used for the diagnosis of disease or medical condition; e.g., monoclonal antibodies and DNA probes are useful diagnostic products.

diagnostic index Frequency of patients with a specific disease among the total number of patients seen at a trial centre; such lists or estimates are important for

assessments of the recruitment potential; see also AGE-SPECIFIC RATE, PREVALENCE, RECRUITMENT RATE.

dialysis Removal of substances from circulation by extracorporeal measures; drugs with small VOLUME OF DISTRIBUTION and low PROTEIN BINDING are usually well dialysable; see also ADME, EXCRETION.

diary card see PATIENT DIARY.

diastereoisomers are STEREOISOMERS that are not ENANTIOMERS and thus not mirror images of each other; see also CHIRALITY.

dichotomous data see NOMINAL DATA.

dietary supplement syn. nutritional supplement, see FOOD SUPPLEMENT; see also FUNCTIONAL FOOD, NUTRACEUTICAL.

Digital Object Identifier (DOI) The DOI System is an ISO International Standard for identifying content objects in the digital environment, managed by the International DOI Foundation; DOI® names are assigned to any entity for use on digital networks; they are used to provide information where they can be found on the Internet; information about a digital object may change over time, including where to find it, but its DOI name will not change; see <http://www.doi.org/>; see also CITATION STYLE.

digital pen see ELECTRONIC CRF.

digital signature FDA "a type of ELECTRONIC SIGNATURE based upon cryptographic methods of originator authentication, computed by a set of rules and a set of parameters that permit verification of the signer's identity and the data's integrity" (21 CFR 11); used in lieu of a physical signature; see also COMPUTERISED SYSTEMS, ELECTRONIC SIGNATURE.

diluants see EXCIPIENTS.

diploma in pharmaceutical medicine In some countries (e.g. Belgium, Germany, Mexico, Spain, Switzerland, UK) postgraduate education in ph.m. is offered with the possibility to get a master's degree, a diploma, or a PhD; see also INTERNATIONAL FEDERATION OF PHARMACEUTICAL PHYSICIANS.

directive (Dir) Term used for documents in the EC which are legally binding in contrast to a GUIDELINE; directives are binding for Member States as regards the objective to be achieved but leave it to the national authorities to decide on how the agreed Community objective is to be incorporated into their domestic legal systems; in contrast to a REGULATION, the aim is not the unification of the law, but its harmonisation in order to remove contradictions and conflicts

between national laws; d. oblige Member States to adapt their national law in line with Community rules; a Dir may be frequently updated: e.g., Dir 2001/83/EC has been amended by Dir 2002/98, Dir 2003/63, 2004/24, 2004/27, Dir 2008/29, 2009/53, 2009/120, 2010/84, 2011/62; see EC LAW, REGULATION.

Direct Health Care Professional Communication (DHPC) Often used synonymously with "Dear Doctor/Prescriber Letter" or "Dear Pharmacist Letter" resp.; provision of information to health care professionals through letters or other means such as the company's website concerning the safe and effective use of a medicinal product; the content may be restricted to safety aspects of a drug such as recall, suspension or withdrawal of the product or important changes to the SPC in relation to safety or availability; see also RISK MANAGEMENT SYSTEM, SAFETY COMMUNICATION.

direct medical costs Fixed and variable costs associated directly with a health care intervention (e.g. payments for drugs, treatments, laboratory and other medical services, costs for staying in the hospital, honoraries); see ECONOMIC ANALYSIS.

direct non-medical costs Costs associated with provision of medical services (e.g. costs for transport of a patient to a hospital, payments for a housekeeper); see ECONOMIC ANALYSIS.

direct patient reporting Australia, Canada, USA and countries of the EC (e.g., Denmark, Italy, the Netherlands, UK) encourage consumers (patients or persons caring for them) to report suspected ADVERSE REACTIONS directly to the health authority ("CONSUMER REPORT").

direct-to-consumer (DTC) In most countries DTC-advertising of PRESCRIPTION DRUGS mandate prior approval of the content by regulatory authorities or are regulated in other ways resp. to protect consumers from false or misleading advertising.

direct-to-consumer advertising (DTCA) In Europe, direct-to-consumer advertising of prescription drugs is still forbidden.

disabilities WHO: "restrictions or lack of ability to perform an activity in a manner or within a range considered normal for a human being"; see also DISEASE, HANDICAP, HEALTH, ILLNESS, IMPAIRMENT.

disclosure procedure Also: code breaking procedure; NLN: "procedure designed to identify, in the event of an emergency, the nature of the treatment given to a SUBJECT"; d. is rarely justified in clinical trials (availability of a drug-specific antidote, reassessment of safety profile); reasons for code breaking as well as when and by whom should always be stated in the CASE RECORD FORM;

after breaking the code the trialist is not blinded any more and the patient must be withdrawn from the study; see also BLINDING.

discontinuation criteria see STOPPING RULES.

disease Abnormal, scientifically verifiable process occurring in the body; WHO recommends that consequences of diseases be classified according to "IMPAIRMENTS" (neurologic abnormalities), "DISABILITIES" (physical incapacity), and "HANDICAPS" (societal impact); see also CONDITION, ILLNESS, ORPHAN DISEASE.

disease free interval (DFI) syn. Disease free survival (DFS); term recommended to describe the period during which there is no evidence of disease activity; it is calculated from the day of surgery to the first day of recurrence; see also DISEASE LATENCY, TUMOR STAGING.

disease free survival (DFS) see DISEASE FREE INTERVAL.

disease latency Time interval between an increment of exposure and a subsequent change in an individual's risk; see also DISEASE FREE INTERVAL.

disease management syn. medical management, therapy management, disease-state management; sometimes also called population-based care, systems management; strategic approach to healthcare for a disease state that attempts to optimise health outcomes within available resources (best medical practice with the least expenditure); model of care directed to prevent or to manage treatment of a disease by maximising the effectiveness and efficacy of care delivery and minimising expenditures of money, time and effort; see also COST/BENEFIT ANALYSIS, DISEASE, EVIDENCE-BASED MEDICINE, NAIROBI PRINCIPLE, OUTCOME MEASUREMENT, OUTCOMES RESEARCH, PERSONALISED MEDICINE, QUALITY OF LIFE.

disintegrants substances with swelling properties in water (e.g. carboxymethylcelluloses), which are used in small amounts to improve tablet disintegration and dissolution; see also DISINTEGRATION TEST, DISSOLUTION TEST, EXCIPIENTS, FORMULATION.

disintegration test In vitro test measuring time to disintegration of tablets under standardized conditions; see also DISSOLUTION TEST, FORMULATION.

disproportionality assessments Data mining algorithms that are basing on disproportionate reporting of an adverse event of interest across different medicinal products; a simple statistical method would be the "Proportional Reporting Ratio", $PRR = [A/(A+B)]/[C/(C+D)]$, i.e. the proportion of reports for a specific suspected adverse reaction (AR) for a given drug compared with the proportion for the same reaction for all other drugs, or the Reporting Odds

Ratio, ROR = (A/C)/(B/D), or the Yule's Q-ratio = (AD − BC)/(AD + BC); see DATA MINING, SIGNAL DETECTION.

	AR of interest	All other events	All ARs for drug
Drug of interest	A	B	A + B
All other drugs	C	D	C + D
AR for all drugs	A + C	B + D	–

In the queries of the EUDRAVIGILANCE Data Analysis System the following criteria are applied to define a SIGNAL of disproportionate reporting: (a) When the PRR is displayed with its 95 % confidence interval: (i) the lower bound of the 95 % confidence interval greater or equal to one; (ii) the number of individual cases greater or equal to three, or (b) when the PRR is displayed with the χ^2 statistic: (i) the PRR > 2; (ii) the $\chi^2 > 4$; (iii) the number of individual cases greater or equal to three; see also BAYESIAN ADVERSE REACTION DIAGNOSTIC INSTRUMENT (BARDI).

disqualification rate see INEVALUABILITY RATE.

dissolution test In vitro test measuring time to dissolution of tablets or capsules under standardized conditions, e.g. artificial gastric juice; dissolution rates correlate with in vivo availability of drug ingredient(s); see also BIOAVAILABILITY, DISINTEGRATION TEST, FORMULATION.

distomer Stereoisomer (out of two enantiomers) that is biologically less potent for a given effect/receptor in contrast to the eutomer having the desired activity; see CHIRALITY, ENANTIOMER, STEREOISOMER.

distribution see VOLUME OF DISTRIBUTION.

distribution of data Dependent on the frequency, DATA can be distributed either normally (i.e. symmetrically around the arithmetic mean, in a bell-shaped or Gaussian curve) or skewed (i.e. with a right-/left-hand tail of higher/lower values); examples for roughly normally distributed data (continuous quantitative measurements): haematocrit, haemoglobin, platelet, blood sugar, heart rate a.s.o., for positively skewed data (to the right): plasma urea, creatinine, catecholamines a.s.o., for negatively skewed data: plasma albumin a.s.o.; frequently statistical tests require normally distributed data (e.g. F-test, t-test); if tests of distribution show that data are not normally distributed, then logarithmic transformation can render data often more normal; otherwise data are analysed by nonparametric statistical techniques (e.g. Spearman rank correlation, Mann–Whitney U-test); in normally or symmetrically distributed data description by the mean and STANDARD DEVIATION is appropriate; for skewed data the MEDIAN is a better measure of the center of the

distribution and as a measure of the spread the RANGE itself or the interquartile range (PERCENTILE R.) should be used.

documentation EC (III): "all records in any form (including documents, magnetic or optical records) describing methods and conduct of the trial, factors affecting the trial and the action taken; these include PROTOCOL, copies of submissions and approvals from the authorities and the ETHICS COMMITTEE, INVESTIGATOR(S), curriculum vitae, consent forms, monitor reports, AUDIT certificates, relevant letters, reference ranges, RAW DATA, completed CASE RECORD FORMS and the FINAL REPORT"; other relevant documents as e.g. product analysis certificates must also be considered.

dominante An allele whose expression overpowers the effect of a second form of the same GENE; (incomplete-/semi-dominante alleles produce the same product but in lesser quantity compared to the dominant allele); see also ALLELE, HETEROCYGOUS, HOMOCYGOUS, RECESSIVE.

dosage form Form of the finished pharmaceutical product such as capsule, tablet, granulate, drops, suppository, etc.; see also ACTIVE PHARMACEUTICAL INGREDIENT, FORMULATION.

dosage regimen Number of prescribed doses (e.g. in capsules of a specified STRENGTH, mg or ampoules, ml) within a given time period.

dose escalation study syn. dose titration study; application of increasing doses of a new substance in human subjects in PHASE I trials; the starting dose is usually calculated on the NO OBSERVED ADVERSE EVENT LEVEL (NOAEL) or the MINIMUM ANTICIPATED BIOLOGICAL EFFECT LEVEL (MABEL), the increase as "single ascending dose" or "multiple ascending dose" design (each patient is titrated to the maximal tolerated dose, e.g., cytostatics); a widely accepted technique uses a modified FIBONACCI SEARCH SCHEME with initially rapid, but smaller dose increments at higher dose levels which might show to be more toxic; e.g. in oncology, the MAXIMALLY TOLERATED DOSE (MTD) is usually reached with such a scheme in about nine escalations (e.g.: 1, 2, 3.3, 5, 7, 9, 12, 16 mg/m^2); other dose escalation schemes proposed are: the MAXIMUM TOLERATED SYSTEMIC EXPOSURE (MTSE), PHARMACOKINETICALLY GUIDED DOSE ESCALATIONS (PGDE), and the CONTINUOUS REASSESSMENT METHOD (CRM); generally about three subjects are treated at each non-toxic dose level; to avoid problems of eventual cumulative effects, subjects are usually exposed to not more than one dose level; see also STAGGERED DOSING APPROACH, PHASE I.

dose proportionality study Study which purpose is to demonstrate linearity (or lack of it) of BIOAVAILABILITY of a drug with increasing doses; see also DOSE ESCALATION STUDY.

dose response relationship In general, the EFFECT of a DRUG can be considered to be proportional to its dose; the documentation of such a relationship is important in early investigations of drug effects; effects with many drugs such as biological substances as e.g. interferons may go through an optimum, i.e. decreasing with increasing doses or fear reduction with low doses of dronabinol but anxiety with high doses; see also PHASE I.

dose titration study see DOSE ESCALATION STUDY.

dosing schedule see TREATMENT SCHEDULE.

double blind see BLINDING.

double data entry see DATA ENTRY.

double coded see CODE.

double-dummy technique When drugs cannot be formulated in a way that galenical forms result which are identical in size, shape, colour, taste, smell a.s.o. then PLACEBO forms identical to each active drug may be produced; disadvantage: the number of e.g. tablets is increased, reducing COMPLIANCE of patients; see also BLINDING.

double masked see BLINDING.

draize tests Single exposure irritancy test for topical drug preparations and COSMETICS, usually applied on rabbit skin or eyes; see also TOXICITY TESTS.

dropouts Subjects not finishing a clinical study for other reasons than such which are clearly study related (e.g. subject revokes consent, transfer to other unit, intercurrent illness, unrelated death, emigration etc.), in contrast to WITHDRAWALS (study related) or LOSS TO FOLLOW-UP (premature termination, no reason known); in long-term trials the d-o. rate will be at least 4 % per annum but the overall d.-o. rate/loss to follow-up rate should not exceed 20 %; in a 3 month trial the number of dropouts should be less than 10 %; the higher the dropout rate the greater the chance that some variable related both to dropping out and to the outcome in question may BIAS study findings (groups are no longer comparable); there is always the risk of a preferential d-o of worsening patients; see also BIAS, EXTENDER ANALYSIS, INEVALUABILITY RATE, INTENT-TO-TREAT, LOSS TO FOLLOW-UP, RUN-IN PERIOD, WITHDRAWALS.

drug FDA: (1) substance recognized in the Official US Pharmacopoeia, Official Homeopathic Pharmacopoeia, or Official National Formulary, or any supplement of them; (2) article intended for use in diagnosis, treatment or prevention of disease, (3) article intended to affect the structure or any function of the body of man or animals, (4) article intended for use as a component of any article

specified in (1), (2), (3); the term "drug" is frequently preferred for describing products with a single (active) component, otherwise the term "product" is used; in European regulations, the term medicinal product or investigational medicinal product is often used synonymously to drug and covers chemical entities, pharmaceutical products bio-technology derived medicinal products and vaccines; see also COMPONENT, ETHICAL DRUG, INVESTIGATIONAL MEDICINAL PRODUCT, NEW DRUG DEVELOPMENT PLAN, OLD SUBSTANCE.

drug abuse EC: "persistent or sporadic, excessive use of drugs inconsistent or unrelated to the recommendation on the SUMMARY OF PRODUCT CHARACTERISTICS or acceptable medicinal practice"; see also MISUSE.

drug accountability Written account of clinical supply use (i.e. receipt date and quantity, date and quantity dispensed, identification of subject who received it, date and quantity returned to SPONSOR or alternate disposition – in this case a copy of authorization received from sponsor is necessary – who is authorized to administer the DRUG, storage conditions etc.); in general detailed calculations are avoided unless it is apparent that improprieties are involved; records may also be useful in case of product recall; see also RECONCILIATION.

drug channelling Selective or high prescription of a drug in a particular subset of patients, e.g. with special prognostic characteristics or degrees of disease severity; examples are: channelling of NSAIDs to patients with peptic ulcer disease, preferential use of certain inhaled beta-2 agonists in patients with more severe asthma a.s.o.; d.c. can cause serious BIAS (allocation bias) in CASE–CONTROL STUDIES; see also PRESCRIPTION-SEQUENCE ANALYSIS.

drug comparability study Study similar to BIOEQUIVALENCE study, except that the purpose is to demonstrate the lack of equivalence of two FORMULATIONS.

drug consumption The approximate number of drug packages per inhabitant were in 2007 (1995): Austria 23 (19), Belgium 22 (23), Denmark 15 (11), Finland 17 (18), France 52 (51), Germany 18 (21), Greece 34 (22), Italy 29 (25), Ireland 23 (12), The Netherlands 14 (11), Portugal 25 (21), Spain 27 (25), Sweden, 17 (15), United Kingdom 23 (14), see also COSTS, MEDICAL CULTURE, PHARMACEUTICAL EXPENDITURE.

drug delivery The process by which a formulated drug is administered to the patient; traditional routes have been orally, intravenous perfusion or by inhalation; new methods that are being developed are through the skin by application of a TRANSDERMAL PATCH, across the nasal membrane or buccal mucosa or by administration of a specially formulated aerosol spray; see also FORMULATION.

drug delivery systems (DDS) Systems which are designed e.g. for improving poor absorption, non-compliance of patients, or inaccurate targeting of therapeutic agents, e.g. topical release systems such as transdermal patches (having the advantage that they are not subject to FIRST-PASS metabolism) or iontophoresis, parenteral drug delivery (depot injections, osmotic pumps, pulse infusion pumps, bio-degradable polymer carriers), inhalation therapy (such as POWDER INHALERS), carrier based delivery (e.g. lipid based systems, liposomes, gene therapy, monoclonal antibodies), by size (micro- or nanoparticles, also called microspheres or nanospheres) or photodynamic therapy to treat cancer; see also FIRST PASS EFFECT, FORMULATION, MEDICAL DEVICE, MICROPARTICLES, NANOPARTICLES, ROUTE OF ADMINISTRATION, TRANSDERMAL PATCH.

drug dependence WHO: "a state, psychic and sometimes physical, resulting from the interaction between a living organism and a DRUG, characterised by behavioural and other responses that always include a compulsion to take the drug in a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence".

drug development see RESEARCH & DEVELOPMENT.

drug error see MEDICATION ERROR.

drug evaluation cost see NEW DRUG APPLICATION; see also MARKETING AUTHORISATION.

drug event combination (DEC) syn. drug-event association, drug-event pair, "Adverse Drug Event" (ADE) = a medication related to an adverse event; an Individual Case Safety Report may be a true, positive DEC (if the relation is confirmed); see SIGNAL.

drug event monitoring see PRESCRIPTION EVENT MONITORING.

drug experience report Report on an ADVERSE REACTION; see also REPORT.

druggable genome GENE (usually corresponding to a protein specific for a disease) that can be modulated by a drug; about 3,000 genes are assumed to be "druggable"; see also GENOME.

drug holiday Non-compliance; the patient interrupts a prescribed treatment for a couple of days or longer without telling his physician; see COMPLIANCE.

drug injury It is estimated that around 1 in 100 prescriptions leads to moderate, 1 in 2,000 to severe side effects and 1 in 1,500,000 to fatalities; women are

more often affected than men and older patients more often than younger subjects; see ADVERSE REACTION, PHARMACOVIGILANCE.

drug interaction probability scale (DIPS) Scale to estimate the probability that an adverse reaction was caused by an interaction (IA) of the drugs in question; according to the total score of ten questions the relationship is doubtful (<2), possible (2–4) or probable (5–8); (Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41:674–680); see also NARANJO NOMOGRAM.

Determining the probability of interaction	Yes	No	Score
Are there previous credible reports of this interaction (IA) in humans?	+1	−1	
Is the observed IA consistent with the known interactive properties of the precipitant drug?	+1	−1	
Is the observed IA consistent with the known interactive properties of the object drug?	+1	−1	
Is the event consistent with the known or reasonable time course of the IA (onset and/or offset)?	+1	−1	
Did the IA remit upon dechallenge of the precipitant drug with no change in the object drug?	+1	−2	
Did the IA reappear when the precipitant drug was re-administered in the presence of continuous use of the object drug?	+2	−1	
Are there reasonable alternative causes for the event?	−1	+1	
Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed IA?	+1	0	
Was the IA confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	
Was the IA greater when the precipitant drug dose was increased or less when it was decreased?	+1	−1	
Total score: doubtful (<2), possible (2–4), probable (5–8); highly probable >8			

drug list Within the EC a "List of the names, pharmaceutical forms, strengths of the medicinal products, routes of administration, marketing authorization

holders in the member states" exists; see COMMUNITY REGISTER, FORMULARY, NATIONAL DRUG LIST, POSITIVE LIST.

drug master file (DMF) Detailed information on a new substance submitted to regulatory authorities for obtaining marketing approval; contains e.g. also important know-how concerning the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method, and on quality control during manufacture. see also INFORMED CONSENT APPLICATION.

drug monitoring (1) continuous measurements of drug concentrations in biological fluids or tissues for therapeutic or safety reasons; (2) registry enrolling patients who are subject of a specific treatment (e.g. every American treated with thalidomide for leprosy is required to enrol in a government/FDA-monitored registry); (3) see POST-MARKETING SURVEILLANCE.

drug product Finished dosage form (e.g. tablet, capsule, solution, etc.) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients; see also DRUG SUBSTANCE, FORMULATION.

drug registration fees see MARKETING AUTHORISATION.

drug repositioning syn. drug reprofiling, therapeutic switching; process of developing new indications for existing drugs; see also LIFE CYCLE MANAGEMENT, RESEARCH & DEVELOPMENT, SERENDIPITY.

drug safety monitoring (DSM) Active surveillance for drug safety (in contrast to SPONTANEOUS REPORT SYSTEM); active surveillance systems usually have higher response rates than "passive" systems such as the YELLOW CARD PROGRAMME; see also PHARMACOVIGILANCE, POST-MARKETING, PRESCRIPTION-EVENT MONITORING, SURVEILLANCE.

drug sales Drug sales (in million US$) in the top seven European pharmaceutical markets were in 1995 as follows: Germany 16.4, France 14.3, Italy 7.5, UK 6.0, Spain 4.6, Netherlands 2.0, Belgium 1.9; US: 52.5, Canada: 3.4, Japan: 26.8; the five leading therapeutic category in the seven top European markets are cardiovasculars (11.7), alimentary/metabolism (9.1), CNS (6.2), anti-infectives (5.3), and respiratory agents (5.2); the pharmaceutical market value (ex-factory prices) increased in Europe from 86,704 (year 2000) to 153,373 (2010), payment for pharmaceuticals by statutory health insurance systems (ambulatory care only) from 76,909 to 120,650; (http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA%20Figures%202012%20Final.pdf).

drug safety unit (DSU) Department within a pharmaceutical company which is responsible for collecting and processing of ADVERSE REACTION reports.

drug substance syn. active substance, ACTIVE PHARMACEUTICAL INGREDIENT; see also DRUG, DRUG PRODUCT.

drug safety updates periodic document prepared by the marketing authorisation (MA) holder, containing all relevant safety information; it should fulfil the following format and content: introduction, CORE DATA SHEET, the drug's licensed status for marketing, update of regulatory or MANUFACTURER actions taken for safety reasons, patient exposure, individual case histories, older studies, overall safety evaluation, important information received after DATA LOCKPOINT; drug safety updates are to be prepared for all authorised medicines at the following intervals: 6-monthly for the first 2 years after authorisation, annually for the subsequent 3 years, thereafter 3-yearly at the time of renewal (EC); see PERIODIC SAFETY UPDATE REPORTS (PSUR).

drug utilisation review (DUR) Process where the use of drugs in individual patients is reviewed by specially trained physicians or other personnel in order to support rational drug therapy.

drug utilisation study Study to establish how rational are drug prescriptions (how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcome); see also MEDICAL AUDIT.

Du Bois formula see BODY SURFACE.

duplicate (ICSR) report same suspected adverse reaction reported by different sources; d.r. can significantly distort potential SIGNALS; see INDIVIDUAL CASE SAFETY REPORT, MASTER REPORT.

E

early-escape design see DESIGN.

EC birth date First date on which the first EC authority (national, EMA) has authorised a new product for marketing within the EC; see also HARMONISED BIRTH DATE.

EC declaration of conformity Depending on the classification of a MEDICAL DEVICE, the manufacturer must ensure application of a quality assurance system; for class I devices, with a low level of vulnerability, conformity assessment procedures can be carried out under the sole responsibility of the manufacturer; for class IIa devices, the intervention of a notified body should be compulsory at the production stage; for devices falling within classes IIb and III which constitute a high risk potential, inspection by a notified body is required with regard to the design and manufacture of the devices; whereas class III is set aside for the most critical devices for which explicit prior authorization with regard to conformity is required for them to be placed on the market; approved for the design, manufacture and final inspection of the products concerned and is subject to audit as well as to Community surveillance; the declaration of conformity is the part of the procedure whereby the manufacturer who fulfills the obligations mentioned above ensures and declares that the products concerned conform to the type described in the EC TYPE-EXAMINATION CERTIFICATE; the declaration must cover quality examination of each product or a representative sample of each batch (product quality assurance), quality assurance techniques at the manufacturing stage particularly as regards sterilization (production quality assurance) or quality assurance at every stage (full quality assurance); among other things, the declaration contains a technical documentation (general description of the product, results of risk analysis, description of ensuring sterile conditions – if applicable, results of

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inspections, test reports, clinical data, label, instructions for use, etc.) in order to allow assessment of conformity; see also EC TYPE-EXAMINATION; see also DEVICE, MEDICAL DEVICE.

EC law Differentiates between DIRECTIVES and REGULATIONS; d. need to be implemented in the national law of each member state before having any force of law (e.g. guidelines on GOOD CLINICAL PRACTICE are "directives"), whereas r. have direct and immediate force of law in all member states. Notes for guidance, guidelines, agreements, decisions, etc. have no legally binding character at all.

ECOG performance status see PERFORMANCE.

ecological fallacy ERROR in interpreting associations between ecological indices; it is committed by mistakenly assuming that because the majority of the group has the characteristic, the characteristic is related to the health state that is common in the group; see also BIAS, CORRELATIONAL STUDY, ECOLOGICAL STUDIES.

ecological study Study comparing the extent of disease and exposure in different populations; interpretation of associations between disease and exposure may result in ECOLOGICAL FALLACY; see also EPIDEMIOLOGY, LARGE SIMPLE DESIGN, RECORD LINKAGE.

economic analysis syn. pharmacoeconomic study; overall term for analyses such as COST/EFFECTIVENESS A., COST/UTILITY A., and QUALITY OF LIFE studies; outcomes measured are e.g. direct medical costs such as payments for drugs, treatments, laboratory and other medical services, direct non-medical costs (related to illness) such as payments for transportation or housekeeper, indirect costs such as lost of earnings due to morbidity and mortality, and intangible costs such as those associated with pain and suffering; examples for cost-effective medical decisions are vaccinations against viral infections or introduction of inhaled steroids for asthma treatment which decreased overall treatment costs by 22 %; some health authorities require economic data to support product application and reimbursement by the national formularies e.g. Australia (since January 1993) and Canada ("Ontario Guidelines", since 1994), European regulatory authorities are expected to follow (guidelines under development e.g. in Italy, Spain, UK, US); in many countries (e.g., France), cost/effectiveness and quality of life are decisive criteria for determining prices and reimbursement; economic evaluations may be seen differently by authorities, (e.g. Australia favorises evaluations where indirect costs are excluded); in monetary terms, the contribution of a subject living in a OECD country with a life expectancy of 25 years to the gross national product was estimated by the world trade bank (1995) to amount to 20,000$, contrary to 333$ of a subject of the third world with a life expectancy

of 15 years; see also HEALTH CARE COSTS, MARGINAL COSTS, TIME TRADE-OFF, WILLINGNESS TO PAY.

ecotoxicity Potential toxic effects of man-made chemicals upon the environment; see also TOXICITY.

EC type-examination (of a MEDICAL DEVICE) Procedure "whereby a notified body ascertains and certifies that a representative sample of the production covered fulfils the relevant provisions of the Council Directive 93/42/EEC"; see also EC DECLARATION OF CONFORMITY, EC TYPE-EXAMINATION CERTIFICATE.

EC type-examination certificate (of a MEDICAL DEVICE) Document issued by an authority summarizing the conclusions of an inspection, the conditions of validity and the data needed for identification of the type of devices approved. The relevant parts of the documentation must be annexed to the certificate. A copy is kept by the notified body; see also EC TYPE-EXAMINATION.

EC verification Procedure whereby the manufacturer or his authorized representative established in the European Community ensures and declares that the MEDICAL DEVICES which have been subject to conformity examinations and tests (among other things, examination of every product or statistical control of products by random sampling) conform to the type described in the EC TYPE-EXAMINATION CERTIFICATE.

effect Result of a DRUG or treatment on a specific pharmacological or biological parameter; see also EFFECTIVENESS, EFFICACY.

effectiveness Therapeutic utility of a DRUG or treatment when used by the public at large under uncontrolled, real world conditions, e.g. survival in cancer; see also COST-EFFECTIVENESS, EFFECT, EFFICACY.

effectiveness analysis see INTENT-TO-TREAT ANALYSIS.

effect modifier Variable which increases or weakens an effect, but – in contrast to CONFOUNDERS – does not BIAS the overall estimate of exposure-outcome associations (e.g. living/hygienic conditions, immune status for developing tuberculosis in addition to exposure to Mycobacterium tuberculosis); see also ADJUVANT, INTERACTION OF DRUGS, LEARNING EFFECT, PLACEBO EFFECT.

effect size Differences in outcome measurements between two or more groups, e.g. in STANDARD DEVIATION units, which then are usually calculated by dividing the differences in post-treatment SCORES between the groups by the standard deviation of the control group scores; in "pre-post" evaluations the difference between pre- and post-mean scores is divided by the pretreatment standard deviation; in broad terms, e.s. above placebo (or no treatment) of <0.5 are associated with weak treatments, needing sample sizes of more than 50 to reach

statistical significance; e.s. between 0.5 and 2.0 are associated with the usual range of effective treatments and samples of about 20 subjects will generate p-values of less than 0.05; e.s. >2.0 are associated with large treatment benefits obvious to most of the observers; five to ten subjects will normally be sufficient to generate significant results; see also ANALYSIS, Q-VALUE, SAMPLE SIZE ESTIMATION, STANDARDIZED RESPONSE MEAN.

efficacy Individual (in contrast to EFFECTIVENESS) therapeutic or pharmacological result of a DRUG or treatment in a controlled clinical situation; assessment of e. needs (EC): "specification of the effect parameters to be used, description of how e. are measured and recorded, times and periods of e. recording, description of special analyses and/or tests to be carried out (pharmacokinetic, clinical, laboratory, radiological, etc.)"; e. measurements should be done by objective criteria, and subjective rating such as from "markedly improved" to "aggravated", although still popular in Japan, are more and more abandoned; see also EFFECT, EFFECTIVENESS, EXTRINSIC FACTORS.

EFPIA European Federation of Pharmaceutical Industries and Associations; represents the pharmaceutical industry operating in Europe (http://www.efipia.eu/).

EFSA European Food Safety Authority (http://www.efsa.europa.eu/).

ejection fraction Volume of blood ejected with each beat by the left ventricle, in relation to end diastolic volume; normal: 50–80 %; see also CARDIAC INDEX.

elderly Subjects equal or older than 65 years (EC); there is evidence of a number of physiological changes in elderly subjects: lean muscle mass decreases whereas fat increases by about 20 % compared with the second decade of life; total BODY WATER decreases by 17 %, extracellular water by 40 %, plasma volume by 8 %, organ blood flow decreases, as does the CARDIAC INDEX; renal plasma flow and GLOMERULAR FILTRATION decrease by about 50 % between ages 40 and 80 years; multimorbidity becomes also more prominent: the mean number of diseases in patients over the age of 65 years is estimated to be between 3 and 4 in industrialised countries; see also AGE GROUPS, GERIATRIC EVALUATIONS, HEALTH CARE COSTS, PRESCRIPTION.

electronic case report form (eCRF) data may be recorded either from SOURCE DOCUMENTS or the eCRF may be used as the primary source document; an alternative may be the use of a digital pen that uses a pen with a tiny camera that tracks pen strokes relative to barely visible dots on a paper form and stores the information electronically; in any case, data must always remain under the control of the investigator and systems as well as procedures must be in place to guarantee that the data are not changed or manipulated; see also CLINICAL

TRIAL, DATA TRANSFER, ELECTRONIC CRF, ELECTRONIC DATA, RAW DATA, SOURCE DATA.

electronic data Electronic data can be recorded on a durable electronic medium such as a hard disk, floppy disk, zip disk, CD-Rom, or tape but also on non-durable media such as personal digital assistants; volatile data are lost when battery power expires; usually a print-out cannot fully substitute for electronic files as metadata may be lost (e.g., author of the data); a certified copy may be acceptable if it is created before the data leave the control of the investigator; see also COMPUTERISED SYSTEMS, REMOTE DATA ENTRY, SOURCE DATA.

electronic data capture (e-DC) synonymously used with REMOTE DATA ENTRY; collecting data in (permanent) electronic form by systems that are modem-, web-based or that involve optical character recognition, audio text, INTERACTIVE VOICE RESPONSE, graphical-clinical laboratory or other interfaces with or without a human interface; any changes to such data must be subject of a complete audit trail; see also COMPUTERISED SYSTEMS, REMOTE DATA ENTRY, SOURCE DATA, WEB-BASED DATA ENTRY.

electronic record FDA: "any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system" (21 CFR 11); see also COMPUTERISED SYSTEMS.

electronic signature OECD: "The entry in the form of magnetic impulses or computer data compilation of any symbol or series of symbols, executed, adapted or authorized by a person to be equivalent to the person's handwritten signature" (i.e. physical signature); FDA "a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's signature" (21 CFR 11); see also COMPUTERISED SYSTEMS, DIGITAL SIGNATURE, OPEN SYSTEM.

eligibility checklist Contains detailed questions which establish a patient's e. for registration on a PROTOCOL; the checklist is created by the biometric department; items included are e.g. demographic information, confirmation of DISEASE (INCLUSION CRITERIA), lab values, performance status, EXCLUSION CRITERIA, date of signed INFORMED CONSENT, etc.

eligibility criteria syn. admission c., entry (entrance) c., selection c.; criteria for defining and selecting SUBJECTS suitable for a CLINICAL TRIAL; a "strict" approach is used to reduce biological inter-patient variability, VARIANCE of outcome VARIABLES and to select patients where maximal effects can be expected (often a more pronounced DISEASE state); a strict approach will therefore increase homogeneity of a study population; a "broad" approach however is

usually followed when only small treatment differences between groups with poor or good prognosis or a small percentage of patients less likely to respond are expected and when speeding up of RECRUITMENT RATES is essential; "loose" e.c. are also often chosen in PHASE IV studies to see how drugs behave on the market under conditions of daily practice; usually e.c. vary considerably according to the indication and the PHASE of a CLINICAL TRIAL (tight during early phases of development, loose in late phases, tight for indications which have a higher chance for spontaneous cure); protocols demanding rigid adherence may yield un-interpretable results because of dropouts and noncompliance emanating from patients and investigator intolerance of the requirements; see also EXCLUSION C., INCLUSION C.

elimination see EXCRETION, see also CLEARANCE, DIALYSIS, HALF-LIFE, KINETIC.

emergency consent waiver see EMERGENCY USE, INFORMED CONSENT.

emergency use Use of a test article on a human SUBJECT in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain INFORMED CONSENT from the patient or legal representative or INSTITUTIONAL REVIEW BOARD (IRB) approval; FDA regulations require that e.u. is reported to the IRB within five working days; any subsequent use of the test article at the institution is subject to IRB review.

emollient Substance used in topical formulations for increasing the hydration of skin, therefore smoothing the surface; see also COSMETIC, FORMULATION.

empiric recurrence risk Risk for family members to develop the same disease/trait as the index patient; risks based on observed DATA rather than theoretical models; see also RISK.

EN 29000 see ISO 9000.

enantiomer STEREOISOMERS which are similar to mirror images of each other having identical physicochemical properties except that they rotate the plane of polarised light in opposite directions by equal amounts; enantiomers which are pharmacologically active are called eutomers, those having not the desired effect ("inactive") distomers; enantiomers often differ in their biologic activity including metabolisation rate, efficacy and safety (e.g., the racemate ofloxacin induces about twice as many haematologic adverse reactions as its enantiomer levofloxacin whereas levofloxacin causes more musculoskeletal disorders); see also AMINO ACIDS, CHIRALITY, RACEMATE, STEREOISOMER.

endocannabinoides Group of neuromodulators (arachidonate-based lipids, e.g. anandamide) that bind to cannabinoid receptors (CB1, CB2 receptors being the most prominent); these receptors are G-protein coupled receptors (GPCRs or GPRs) and mediate also the psychoactive effects of cannabis; E are involved

in a variety of physiological processes, including appetite, immune- and inflammatory processes, pain, motor neuron activity, etc. and resemble the cannabinoids (constituents of cannabis) in many biological properties. The endocannabinoid system is vital for the maintenance of homeostasis and can be found in all higher organisms and organs.

endocrine disrupting chemicals (EDCs) see ALIMENTARY RISKS, EFSA, PESTICIDES.

endorphins E are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise, excitement, and orgasm; and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. E work as "natural fever relievers", whose effects may be enhanced by other medications.

endotoxin test see LIMULUS AMEBOCYTE LYSATE TEST.

endpoint syn. outcome VARIABLE, outcome measurement; see PRIMARY ENDPOINTS, SCALE, SCORE, SURROGATE ENDPOINTS.

enrolment log List to "document chronological enrolment of subjects by trial number" (ICH E6, GCP); see also SUBJECT IDENTIFICATION CODE LIST, SUBJECT SCREENING LOG.

enteral administration Opposite: parenteral a.; see ADMINISTRATION, DELIVERY.

enteric coated tablet (ECT) see ENTERIC COATING, FORMULATION.

enteric coating Coating for oral FORMULATIONS in order to prevent disintegration or inactivation of a drug in the acidic conditions of the stomach.

enterohepatic circulation Drugs which are excreted via bile can be reabsorbed in the jejunum, which increases the BIOAVAILABILITY; see also FIRST PASS EFFECT.

entry criteria see ELIGIBILITY CRITERIA.

environmental risk assessment – consists of two phases. The first phase (Phase I) assesses the exposure of the environment to the active substance and/or its metabolites. In a second phase (Phase II), information about the physical/chemical, pharmacological and/or toxicological properties are obtained and assessed in relation to the extent of exposure of the environment. Phase II is divided in two parts: Tier A begins with an evaluation of the possible fate and effects of the active substance and/or its metabolites (What might go wrong? – What is it's probability? – What are the consequences?). If within Tier A, no risk is detected, there is no need to proceed to Tier B. If a risk is detected, then the fate and effects of the active substance and/or its metabolites in the relevant compartment should be adequately investigated in Tier B. (EMEA 2005,

CPMP/SWP/4447/00); an example for potential environmental risks associated with medicinal products comes from ß-agonists such as clenbuterol (used for treatment of bronchiectasis/ to increase pulmonary ventilation): in amounts 5–10 fold the normal dosage it increases the muscle mass substantially and has therefore been used in animals (now banned in the EC, USA, China). As clenbuterol is stable and not destroyed by general heating it can cause toxicity symptoms; see also AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY (ATSDR), ALIMENTARY RISKS, LOWED PREDICTED ENVIRONMENTAL CONCENTRATION.

enzyme A protein catalyst that facilitates specific chemical or metabolic reactions necessary for cell growth and reproduction.

epidemic Occurrence of a DISEASE on a higher rate than expected, based on past experience; see also EPIDEMIOLOGY.

epidemiology def.: study of the distribution of DISEASES or ADVERSE EVENTS in human populations, and of the factors which influence this distribution; see also CASE-CONTROL STUDY, COHORT STUDY, CORRELATIONAL STUDY, CROSS-SECTIONAL STUDY, DESIGN, ECOLOGICAL STUDY, EVALUATION TECHNIQUE, EXTRA INCIDENCE RATE OF NON-VACCINATED GROUPS, IMMORTAL TIME BIAS, LARGE SIMPLE TRIAL DESIGN, MATCHED PAIR, NEIGHBORHOOD CONTROL SUBJECTS, ODDS RATIO, POST-APPROVAL RESEARCH, REGISTRY, STRENGTHENING THE REPORTING OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY, YELLOW CARD SCHEME.

EQUATOR Network International initiative that aims to enhance the reliability and value of the published health research literature (http://www.equator-network.og); see PUBLICATION GUIDELINES.

equipoise Situation where a trialist is uncertain about which treatment in a parallel DESIGN would be therapeutically superior; see BLINDING.

error Most frequent origin of unreliable DATA; if e.g. errors occur with a frequency of 2 % at each of the following levels: misinterpretation, entry on CASE RECORD FORM, DATA entry in computers, processing, and presentation in reports, only 88.56 % of them would be reliable; other types of e.: sampling e. (improper sample processing, e.g. phlebotomy, non-fasting condition, sample storage/transport); systematic e. (i.e. non-random unidirectional e., e.g. due to sample deterioration, changes of the instrument response or measuring conditions with time); random e. (variations affecting precision of methods at random such as errors of measurement); clerical e. (key-punch e.) (conc. data entry or transfer) systematic technologist/observer e. (different technicians never perform a manual procedure in exactly the same way); laboratory BIAS (e. which arise from basic differences between laboratories that involve

reagents, instrumentation, environment and methods); in CLINICAL TRIALS erroneous data arise most often from protocol-violations (wrong inclusion, unauthorised co-therapy, dosing errors, broken blindness, multiple admission, treatment discontinuation, wrong allocation, poor adherers a.s.o.), rarely also from fraudulent practices; see also ALPHA E., BETA E., BUG, CLERICAL ERROR, CLINICAL HETEROGENEITY, DATA, ECOLOGICAL FALLACY, FRAUD, GAMMA E., MEDICATION E., NEYMAN FALLACY, OUTLIERS, PROGRAMMATIC ERROR, RAW-DATA, SAMPLING ERROR.

error of measurement (E of M) see ERROR.

escape medication see RESCUE MEDICATION.

essential documents Documents absolutely necessary according to GCP for the correct and complete documentation of a clinical trial and kept in the TRIAL MASTER FILE.

essential drug list (EDL) (syn. essential medicines) List of pharmaceutical products deemed absolutely necessary for treatment of patients; issued by national governments (non-listed products may be banned!), but also by the WHO; the EDL of the WHO (edition 2011) lists about 360 (for adults) and 270 (children) pharmaceutical products resp.; http://www.who.int/medicines/publications/essentialmedicines/en/.

essential medicines see ESSENTIAL DRUG LIST.

essential requirements (ERs) Requirements to be fulfilled by a MEDICAL DEVICE before the CE-MARKING can be affixed.

essentially similar products (EC): "A PROPRIETARY MEDICINAL PRODUCT will be regarded as essentially similar to another product if it has the same qualitative and quantitative composition in terms of active principles (substances), and the pharmaceutical form is the same and, when necessary, BIOEQUIVALENCE with the first product has been demonstrated by appropriate BIOAVAILABILITY studies carried out"; this applies also to different oral forms for immediate release, e.g. tablets and capsules (however there is no support for using indications, doses or dosing schedules as additional criterion); see also PHARMACEUTICAL EQUIVALENT, THERAPEUTIC EQUIVALENT; either the original manufacturer has to give permission or the second applicant must be able to show that its "similar" product makes a significant contribution to patient care; this other product must have received marketing authorisation in the EU more than 6 or 10 years ago in the concerned member states in the applied pharmaceutical forms, strengths and route of administration; see also ABRIGED APPLICATION, MARKET EXCLUSIVITY.

establishment licence application (ELA) US term for application for marketing authorisation of well-characterised biotechnology products; see also NEW DRUG APPLICATION.

establishment inspection report (EIR) Result after a FDA-INSPECTION; reports are classified as NAI (no action indicated) = the investigator is in compliance, VAI-1 (voluntary action indicated) = objectionable condition or practice was corrected during the inspection and the conditions had minimal effect on the integrity (validity of data or rights of research subjects) of the study, VAI-2 = objectionable condition or practice has not been corrected during the inspection and the conditions had minimal effect on the integrity of the study; VAI-2C only deficiency found was related to an inadequate consent form; VAI-3 = response to a letter of adverse findings requested or a follow-up inspection initiated; VAI-3R response to a letter of adverse findings has been received and accepted; VAI-3F a follow-up "for cause" inspection initiated; OAI = official action indicated; OAIC = official action taken and/or case closed; WASH = washout, full inspection not conducted; CANC = cancellation, inspection not conducted; see also AUDIT, INSPECTION.

ethical drug signified drugs advertised only to doctors; the expression refers to the original 1847 code of ethics of the AMA, which deemed advertising directly to the public to be unethical; over time, the term came to mean legal drugs (FDA Glossary); see PRESCRIPTION DRUG.

ethics committee (EC) Committee of independent (medical) professionals and non-medical members to which a trial plan is submitted to ensure the rights, safety and integrity of the participants are protected thereby providing public reassurance; according to the EC (III) the e.c. "should be constituted and operated so that the suitability of the INVESTIGATORS, facilities, PROTOCOLS, eligibility of trial SUBJECT groups, and adequacy of confidentiality safeguards may be objectively and impartially assessed independently of the investigator, SPONSOR and relevant authorities". "The composition should be, and a description of its working procedures including response times must be, publicly available. The legal status, constitution, and regulatory requirements may differ among countries"; see also ANNUAL PROGRESS REPORT, INSTITUTIONAL REVIEW BOARD, STEERING COMMITTEE.

ethnic differences human populations can show differences with regard to disease susceptibility, rate of metabolism (extensive/slow/poor METABOLISM), presentation and metabolism of drugs; e.g. sickle cell anemia is much more frequent in people of african origin than kaukasians, chinese people are more susceptible to haloperidol than white patients; average interethnic differences in pharmacokinetic or pharmacodynamic results however are low; see also CYTOCHROM P450, GENOME, METABOLISM, PHARMACOGENETICS.

etiologic fraction (EF) syn. population attributable RISK; proportion of all cases with a specific outcome and attributable to exposure of a target population; EF = (Rt – Re)/Rt whereby Rt = risk of outcome in the target population, Re = risk in an unexposed population.

EU birth date (EBD): "date of first marketing authorisation granted for the medicinal product in any EU member state to the Marketing Authorisation Holder (MAH)"; the MAH may use the IBD to determine the dates of the datalock points for PERIODIC SAFETY UPDATE REPORTS (PSUR) submission schedule, provided that the first datalock point falls within 6 months following the EBD; (EUDRALEX Vol 9A); see also HARMONISED BIRTH DATE, INTERNATIONAL BIRTH DATE.

EudraCT EMA's reporting program for clinical trials; all clinical trials conducted in the EC must be registered in the EudaCT data base (http://eudract.emea.europa.eu), where each CT receives a unique number (extensions used for resubmission: A for first resubmission, B for the second a.s.o); the number of trials registered varies but has declined from roughly 9,300 in 2008 to 5,900 in 2010, with more than 60 % sponsored by the pharmaceutical industry; up to 2011, 8 versions have been released between 2004 and 2011 (not counting multiple amendments of each version); part of the database is open to the general public (EudraPharm); the website provides also access to directives, guidelines and user documentation; see also CLINICAL TRIAL REGISTER.

EudraPharm Stands for: European Union Drug Regulating Authorities Pharmaceutical Database; data base of all medicinal products with a marketing authorisation in the European Community; the data base includes the Summary of Product Characteristics; part of the database is open to the general public (EudraPharm); http://eudrapharm.eu/eudrapharm/; see also CLINICAL TRIAL REGISTER.

EudraVigilance EMA's reporting program for adverse reactions (EVWEB), existing since December 2001 and mandatory since November 2005; the data set is sent to the EudraVigilance electronically, at present only reports that have been confirmed by a healthcare professional; the EudraVigilance program consists of two modules, (i) the EVPM –post marketing/post authorisation module related to ICSRs that need to be reported according to Regulation (EC) No. 726/2004, Directive 2004/27/EC and taking into account Volume 9A and (ii) the EVCT-clinical trial module, for all SUSARs that need to be reported (by the company) in accordance with Directive 2001/20/EC and Volume 10; the EudraVigilance Medicinal Product Dictionary (**EVMPD**) is basically an extension and exists since 2005; it was replaced by Extended Medicinal Product Dictionary (**XEVMPD**) that is mandatory from 02 July 2012; MAH are also requested to submit directly side effects of their products and must use the eXtended EudraVigilance Medicinal Product Report Message (**XEVPRM**) as format; registration with EudraVigilance is a prerequisite for both systems; the person who should register is the QUALIFIED PERSON for Pharmacovigilance (Article 103 of Dir 2001/83/EC, Regulation (EEC) No 2309/93); submission of information by MAH is either electronically via a web portal (EVWEB, Webtrader) or manually; programs similar to the EudraVigilance are the "Canada Vigilance Program" and "MEDWATCH" (USA); the EurdaVigilance database

allows (restricted) access to the public; see also EU RISK MANAGEMENT PLAN, INDIVIDUAL CASE SAFETY REPORT, PHARMACOVIGILANCE.

EudraVigilance data base EMA's data base of adverse reactions (http://www.adrreports.eu/); it is expected that marketing authorisation holders, national competent authorities and EMA is continuously monitoring the data to determine whether there are new RISKS or whether risks have changed and whether this has an impact on the current BENEFIT-RISK balance of the respective medicinal product; health care professionals and the public have restricted access in 2010 the data base contained over 2,2 mio spontaneous reports and some 400,000 SUSARs; see also EUDRAVIGILANCE, EU RISK MANAGEMENT PLAN, PHARMACOVIGILANCE.

EudraVigilance Medicinal Product Dictionary (EVMPD) The EVMPD is basically a compilation of information to a specific medicinal product authorised in the EC and exists since 2005; it was replaced by Extended Medicinal Product Dictionary (XEVMPD) that is mandatory from 02 July 2012 (Reg 726/2004) and creates – in contrast to the voluntary EVMPD – a list of all medicinal products authorised/registered within the European Community as well as on products under development for which a EVCODE must be obtained (the EV Code is the unique reference for a product and the pertinent information in the EMA database); each strength counts as one product; XEVMPD requests much more additional information on medicinal products than just on safety, basically the information given also in the SPC (e.g., ATC-code, MAH, marketing authorisation number, marketing authorisation procedure, therapeutic indications granted as MedDRA codes, excipients, etc.) as well as the printed product information (SPC, PIL, labelling) as a separate document; see also EUDRAVIGILANCE.

EU Risk Management Plan (EU-RMP); see RISK MANAGEMENT PLAN.

European Medicines Agency (EMA), former: EMEA – European Medicines Evaluation Agency; Registration authority within the EC and coordinating centre for the CENTRALISED PROCEDURE, sited in London; roughly 85 % of the annual budget (estimation of 2011, increased from 76 % in 2010) is financed by the pharmaceutical industry by revenues from services rendered such as fees for application for marketing authorization, inspection, PHARMACOVIGILANCE activities (e.g., up to € 80,300 for the assessment of each PSUR, € 80,300 for a marketing authorization application in the CENTRALIZED PROCEDURE, € 80,300 for the assessment of each final study report for POST-AUTHORISATION SAFETY STUDIES, € 80,300 for a type II variation procedure, etc.), scientific advice and the like; all fees are adjusted annually to the inflation rate; (2010: total expenditures € 203 mio, revenues from services 154 mio); see also EXPERT DÉTACHÉ.

European database of suspected adverse reaction reports EMA operates a public and searchable "European database of suspected adverse reaction reports" (http://www.adrreports.eu/).

European Medicines Evaluation Agency (EMEA) renamed to European Medicines Agency (EMA); see EUROPEAN MEDICINES AGENCY.

European Pharmacopoeia (Eur Ph) Pharmacopoeia published by the Council of Europe; see INTERNATIONAL NON-PROPRIETARY NAME, PHARMACOPOEIA.

European Public Assessment Report (EPAR) Report which summarizes the regulatory decisions made by the European Commission (the legal authority for EMA authorisations) concerning MARKETING AUTHORISATION of a new drug.

European Union Reference date syn: Union Reference Date; "date of first marketing authorization in the EU of a medicinal product containing that active substance or that combination of active substances"; see also HARMONISED BIRTH DATE, INTERNATIONAL BIRTH DATE.

eutomer see CHIRALITY, ENANTIOMER.

evaluation report see AUDIT.

EVCODE see EUDRAVIGILANCE.

event timing see INCIDENCE.

evidence based medicine (EBM) Conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (Brit Med J 1996:312:71–72); evidence-based medicine relies on well conducted studies as well as on empirical data; see DISEASE MANAGEMENT, FRAMINGHAM STUDY, OUTCOMES RESEARCH.

evidence based prescribing An approach to practising medicine whereby care to patients is based on what research says is most effective, rather than tradition, instinct or other factors.

excess incidence def.: portion of subjects who, over a specific time, develop a specific attribute (AR) when exposed to a treatment versus the portion of subjects who develop the same specific attribute when exposed to placebo or another comparator (e.g., in controlled clinical trials); the e.i. is most often used to distinguish between effects of a medicinal product and the "normal" incidence; differences in incidence rates may arise from bias due to the conditions of observations (blinded or open label) or confounders such as dose, gender or age; see also AGE-SPECIFIC RATE, ATTACK RATE, CUMULATIVE INCIDENCE, INCIDENCE RATE, PREVALENCE RATE.

excipient Substances used in powder formulations in order to improve physical properties of the active ingredient; excipients are diluents (providing plug-forming properties, e.g. lactose, mannitol, sucrose, glucose, icing sugar), lubricants (reducing powder/metal adhesion, e.g. stearats, dimethicone, hydrogenated

vegetable oils, liquid paraffin, polyethylene glycol, sodium stearyl fumarate), glidants (improving powder flow e.g. for capsule-filling machines, e.g. colloidal silicon dioxide, Ca silicate), wetting agents (improving water penetration, e.g. sodium lauryl sulfate, lecithin, polysorbate, polyoxyethylene stearate, sorbitan mono-oleate, polyethylene glycol 6000), disintegrants (producing disruption of powder mass, e.g. sodium starch glycolate, alginic acid, croscarmellose, crospovidone, carmellose calcium, sodium carboxyaminopectin) and stabilizers (improving product stability, e.g. ascorbic acid, ascorbyl palmitate, malic acid, propyl gallate, sodium metabisulphite); see ADJUVANT, ANTIOXIDANTS, DISINTEGRANTS, DOSAGE FORM, EUDRAVIGILANCE MEDICINAL PRODUCT DICTIONARY, FORMULATION, PRESERVATIVES; see also www.ipec-europe.org.

exclusion criteria Criteria whereby an individual patient should not be eligible for a specific treatment in a CLINICAL TRIAL; e.c. should be used mainly to exclude patients likely to be harmed by one of the treatments or with conditions that may invalidate the results; see also ELIGIBILITY CHECKLIST, INCLUSION CRITERIA.

excretion Elimination of a drug, either as metabolites or in unchanged form; the kidneys are the most important route for water soluble substances (polar or ionized); some drugs are excreted into bile and excreted via faeces, some however can be reabsorbed into the blood (ENTEROHEPATIC CIRCULATION); volatile substances (anaesthetics, toxic gases) can be excreted through the lungs; additional routes of excretion include sweat, saliva, tears, nasal secretions and milk; see also ADME, CLEARANCE, DIALYSIS, FIRST-PASS EFFECT, GLOMERULAR FILTRATION RATE, HALF-LIFE, KINETIC.

exit interview syn. CLOSING MEETING, DEBRIEFING MEETING, exit debriefing; meeting of an auditor or inspector with the auditees at the end of an audit/inspection where findings and consequences are discussed before a more formal presentation in the report; see also FDA 483 FORM, OPENING MEETING.

expanded-access program Many health authorities regulate formally the conditions under which a larger population of patients could gain expanded access to promising, new investigational DRUGS, early in the development process, e.g. for treatment of cancer or AIDS; programs as available in the US are, e.g. TREATMENT IND for serious or life-threatening DISEASES, COMPASSIONATE USE, emergency/investigator IND, open-label protocol (under an IND, to collect safety data); see also ORPHAN DRUGS; accelerated registration procedures may also exist.

expected (listed) adverse event see UNEXPECTED ADVERSE EVENT.

expedited drug development Alternative to standard DRUG development in order to make promising therapies available sooner; especially for patients who

can neither take standard therapy nor participate in controlled clinical trials; e.d.d. is intended to speed up clinical development, evaluation and marketing approval of new therapies for patients with life-threatening or severely debilitating ILLNESSES, especially where no satisfactory alternative exists; see also COMMUNITY BASED TRIALS, PARALLEL TRACK, TREATMENT IND.

expedited reporting EU: All ARs received from Healthcare Professionals, either spontaneously or through post-authorisation studies, should be reported, regardless of whether or not the medicinal product (MP) was used in accordance with the authorised Summary of Product Characteristics (SPC) and regardless whether they have occurred in the European Union or in a third country by the MAH within 15 days; ICH E2A: "all adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting … (FDA: "alert report"; the sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all ADVERSE DRUG REACTIONS (ADRs) that are both serious and unexpected …; e.r. of reactions which are serious but expected will ordinarily be inappropriate …; e.r. is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not"; "when a serious adverse event is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind"; see also ADVERSE DRUG REACTION, BLINDING, INDIVIDUAL CASE SAFETY REPORT.

expedited review FDA allows e.r. for certain kinds of research involving no more than minimal RISK (e.g. recording data from adults by non-invasive procedures, blood sampling, study of existing data etc.), and for minor changes in research already approved by an INSTITUTIONAL REVIEW BOARD (IRB); the e.r. may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson among members of the IRB; all members have to be kept informed about proposals approved under e.r.

experimental drug DRUG which is under clinical DEVELOPMENT and therefore not registered by any health authority; see also INVESTIGATIONAL DRUG, RESEARCH AND DEVELOPMENT.

experimental trial see CONTROLLED CLINICAL TRIAL.

expert détaché expert who facilitates cooperation between EMA and the national authority.

expert report Each EC DECENTRALISED/MULTISTATE or HIGH-TECH application for marketing authorization shall contain three e.r., critically evaluating and providing an overview on the chemical/biological/pharmaceutical part, the toxicological/pharmacological and clinical part of the file; it consists of a critical

evaluation of the quality of the product and the investigations carried out and enables the reader to obtain a good understanding of, inter alia, the properties, safety, efficacy, advantages and disadvantages of the product; EC (!): "all important data shall be summarized in an appendix to the e.r., whenever possible including report formats in tabular or in graphic form" (with cross references, signed, normally less than 25 pages); these e.r. of the past have been replaced by the module 2 of the COMMON TECHNICAL DOCUMENT that is now standard.

expert system syn. knowledge-based system; decision support program that helps less experienced people to make decisions at or near the level of experts; the basis of such decision-making processes is expertise or knowledge stored in DATA structures called knowledge bases containing "if–then" rules; these rules are then interpreted by another part of the system called an inference engine that contains predefined logic.

expiration date syn. EXPIRY DATE; FDA: "date placed on the immediate container label of a DRUG product that designates the date through which the product is expected to remain within specifications; if the e.d. includes only month and year, it is expected that the product will meet specifications through the last day of the month"; for investigational products the original e.d. may be extended, even during a CLINICAL TRIAL, strictly following the respective STANDARD OPERATING PROCEDURES; see also RETEST DATE, STABILITY TESTS, STERILITY.

expiration dating period FDA: "interval that a drug product is expected to remain within the approved specifications after manufacture".

expiry date (EXP) syn. EXPIRATION DATE; NLN: "date given by the manufacturer in uncoded form, based on the stability of the pharmaceutical product, beyond which it shall not be used"; see also RETEST DATE, STABILITY.

explanatory trial Is the usual attempt to examine the magnitude of treatment effects and to explain observations (either treatment may be superior; $A > B$, $A = B$, $A < B$); see also PILOT STUDY, PRAGMATIC/DECISION-MAKING TRIAL.

exposure data For PERIODIC SAFETY UPDATE REPORTS it is necessary to include data on the number of patients exposed post-marketing; usually these numbers are calculated by the number of packages sold (or other units such as tablets) divided by the average length of treatment time; patient exposure data should preferably be provided as patient-time of exposure (patient-days, -months -years); for the calculation it is important to consider the way a medicine is used (e.g. for chronic treatments the calculation of patient years may be more appropriate); see also PATIENT EXPOSURE.

expression In genetics, manifestation of a characteristic that is specified by a gene; with hereditary diseases, for example, a person can carry the gene for the disease but not actually have the disease in which case the gene is present but

not expressed; in molecular biology and industrial biotechnology, the term is often used to mean the production of a protein by a gene that has been inserted into a new host organism.

Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) see EUDRAVIGILANCE MEDICINAL PRODUCT DICTIONARY.

eXtended EudraVigilance Medicinal Product Report Message (XEVPRM) see EUDRAVIGILANCE.

EVCODE see EUDRAVIGILANCE.

extended release form see PROLONGED RELEASE, see also CONTROLLED RELEASE FORM.

extender analysis A. of DATA of DROP-OUTS according to the INTENT-TO-TREAT PRINCIPLE; e.a. is done with DATA of the last time of observation (last-value-carried-forward); see also ANALYSIS.

extension application extensions of marketing authorization may be related to changes to the active substance (e.g., different salt, replacement by a different isomer, different mixture of isomers) where characteristics are not significantly different, or changes to the strength (such as a new one), form or route of administration; other extensions may be changes to the extraction solvent or changes to strength, pharmaceutical form and route of administration, or a change of bioavailability; see LIFE-CYCLE MANAGEMENT, MARKETING AUTHORIZATION, TYPE II VARIATION.

extension protocol see CONTINUATION STUDY.

external audit Independent audit by a third party; see AUDIT.

extra incidence rate in non-vaccinated groups (EIRnv) Parameter used in vaccination studies in order to assess EFFICACY of a vaccine; usually compared with the incidence rate in vaccinated groups; see also EPIDEMIOLOGY, EXTRA INCIDENCE RATE IN VACCINATED GROUPS, INCIDENCE RATE.

extra incidence rate in vaccinated groups (EIRv) Increased rate of a disease in a vaccinated population; see also EXTRA INCIDENCE RATE IN NON-VACCINATED GROUPS, INCIDENCE RATE.

extrinsic factors In the ICH E5 guideline on "Ethnic Factors in the Acceptance of Foreign Data", factors that may result in different responses to a drug in different populations are categorised as intrinsic ethnic factors (e.g., e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) or extrinsic ethnic factors (e.g., drug-drug interactions, diet, smoking, and alcohol use).

F

factorial design D. where it is possible to answer two (or more) questions for the "price" of one (two interventions are of interest and the application of one does not interfere with the application of the other; i.e. different ENDPOINTS are appropriate for the evaluation, intervention(s) are likely to be ineffective a.s.o.); comparisons can be either between SUBJECTS or within subjects; example: study-DESIGN with four parallel groups, each receiving one specific treatment (A, B, A + B, PLACEBO); this d. gives four estimates for four groups, i.e. two estimates for each drug effect; a standard design would consist of three groups (A, B, placebo) giving an estimate of the effect of A, as well as of B; suitable for "economising" patient numbers and for studying treatment interactions; as this design implicates multiple comparisons it is necessary to perform corrections (BONFERRONI) for the statistical testing.

falsified medicinal product Adverse reactions associated with a suspected falsified m.p. are coded in addition with the MedDRA Lower Level Term code 10071287 ("suspected product counterfeit"); for confirmed falsified m.p. the code 10063180 ("pharmaceutical product counterfeit") is added to the adverse reaction; see also COUNTERFEIT MEDICINE, QUALITY DEFECT. Dir 2011/62/EU ("Falsified Medicines Directive").

fast track procedure see ACCELERATED ACCESS PROGRAMME.

FDA 356h form Form used in the USA for application to market a new drug for human use or an antibiotic drug for human use; see also FOOD AND DRUG ADMINISTRATION, NEW DRUG APPLICATION.

FDA 482 form Form used in the USA notice of inspection; see INSPECTION.

FDA 483 form Form used in the USA for describing inspectional observations at the close of an inspection; see DEBRIEFING MEETING, EXIT INTERVIEW, INSPECTION.

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FDA 484 form Form used in the USA for confirming receipt of samples; see INSPECTION.

FDA 1571 form Form used in the USA for investigational new drug application (cover sheet form); see also INVESTIGATIONAL NEW DRUG.

FDA 1572 form Form used in the USA for the statement of INVESTIGATOR who participates in a clinical trial with an INVESTIGATIONAL DRUG.

FDA 1639 form Form used in the USA for ADVERSE REACTION reporting of drugs and biologics; almost identical to the CIOMS-form; see also CIOMS FORM.

FDA 3455 form Form used in the USA for disclosure of financial interests.

Fibonacci search scheme dose escalation strategy in PHASE I clinical trials in oncology; the genuine F scheme is 1, 2, 3, 5, 8, 13, 21, 34 a.s.o. whereby the next dose is equal to the sum of the two doses before; various modifications exist that are also called "Fibonacci scheme" (e.g., starting dose D1, level two D1 + 100 %, level three D1 + 100 + 67 %, level four D1 + 100 + 67 + 50 %, each further level with additional +30 % of dose D1) with initially rapid, but smaller dose increments at higher dose levels which might show to be more toxic; see also CONTINUOUS REASSESSMENT METHOD (CRM), DOSE ESCALATION, MAXIMUM TOLERATED SYSTEMIC EXPOSURE (MTSE), PHARMACOKINETICALLY GUIDED DOSE ESCALATIONS (PGDE).

field study see MARKETING STUDY.

fifteen days report see ADVERSE REACTION, EXPEDITED REPORTING.

FIGO-staging Staging classification system used to describe size and extent of gynaecological cancers, using the FIGO nomenclature (International Federation of Gynecology and Obstetrics); 0 – carcinoma in situ; I and II – growth limited to the organ; III and IV – tumour invades neighbour organs and lymph nodes; see also CLASSIFICATION OF RECURRENCE, DISEASE FREE INTERVAL, TUMOR-STAGING.

film coating Manufacturing process where tablets (the nucleus) are covered by a thin (organic) film to improve some properties e.g., swallowing (non-functional coating) or the release profile of the active ingredient (functional coating e.g., enteric coating to resist inactivation by gastric juice); traditional non-functional coatings consist of cellulosic derivatives, polymetacrylate or modified pea starch; see also FORMULATION.

final report Complete and comprehensive description of the trial after its completion; includes a description of experimental and statistical methods and materials, presentation and evaluation of results, statistical analyses, and a critical statistical and clinical appraisal (integrated statistical and medical REPORT

of a study); EC guidelines request that f.r.s must be retained by the SPONSOR, or subsequent owner, for at least 5 years beyond the lifetime of his product; FDA recommends a final report to be available within 3 months.

finding (during an audit or inspection) see INSPECTIONAL OBSERVATIONS, OBSERVATION.

fine see SANCTION.

finished product EC (IV): "MEDICINAL PRODUCT which has undergone all stages of production, including packaging in its final container"; see also BATCH DOCUMENTATION, BULK PRODUCT, INTERMEDIATE PRODUCT, PACKAGING, PRODUCTION, STARTING MATERIAL.

first-in-man study First administration of a test article to human subjects; see PHASE I.

first-order kinetics see KINETIC.

first-pass effect syn. pre-systemic hepatic elimination; metabolism of a DRUG before it can reach the systemic circulation, most often due to metabolism in the liver (oral drug), but possibly also on other sites as e.g. the lung, or the gastrointestinal wall; f.-p. effects can be the reason for a non-linear kinetic with an increasing BIOAVAILABILITY with increasing doses of a drug (e.g. propranolol, verapamil, lidocaine); see also ABSORPTION, DRUG DELIVERY, ROUTE OF ADMINISTRATION.

fixed-payment system see PRICE REGULATORY SCHEME, REFERENCE PRICING.

flexible design see ADAPTIVE DESIGN.

floor effect opp. CEILING EFFECT; effects, especially SCORES measured, cannot go beyond a predefined lowest level; therefore observations will accumulate and form a rather inhomogeneous group; results will be heavily skewed (see SKEWNESS).

flow chart syn. time-event schedule; diagram summarizing the various actions (lab tests, physical examinations a.s.o.) to be taken during different visits of a CLINICAL TRIAL.

follow-up protocol see CONTINUATION STUDY.

Fontaine's stages Describe peripheral arterial occlusive disease (PAOD); I = asymptomatic, circulatory reserve is adequate, merely slight changes in the vessel wall; II = circulatory reserve is compromised, IIa walking distance > 200 m (5 km/h), IIb walking distance < 200 m; III = rest pain due to inadequate compensation; IV = necroses, typically in distal regions as toe and foot, with or

without rest pain; Doppler ultrasound pressures over malleolar arteries are less than 50 mm Hg.

food FDA: article used for food or drink for man or animals, incl. chewing gum, and article used as component of any such article; see also ALIMENTARY RISKS, FUNCTIONAL FOOD.

food supplement syn. dietary supplement; food containing concentrated sources of nutrients such as vitamins, minerals or herbal products and presented for supplementing the intake of those nutrients from the normal diet ("fortified food"); however, some products contain chemicals as potent as any drug; in addition, the purity of supplement ingredients may not always be guaranteed, and consumers may harm themselves if they believe "more is better" and exceed manufacturer-recommended doses; this can cause side effects (Dir 2006/46/EC); see also ALIMENTARY RISKS, DRUG, FUNCTIONAL FOOD, HEALTH CLAIMS, NUTRIENTS, ORTHOMOLECULAR MEDICINE, PHYTOMEDICINES, RECOMMEND DIETARY ALLOWANCE, TRADITIONAL HERBAL MEDICINAL PRODUCT.

Food and Drug Administration (FDA) U.S. American regulatory authority responsible for INVESTIGATIONAL NEW DRUGS and for the marketing authorisation of them; see also FDA, NEW DRUG APPLICATION.

forced licensing see COMPULSORY LICENSING.

forest plot graphical presentation of individual results of each study included in a meta-analysis and the combined result; results of individual studies are shown as squares centered on the point estimate of each study whereby a horizontal line trough the point estimate shows the confidence interval (most often 95 %); see also FUNNEL PLOT.

formulary (national) f.; syn drug list, positive list; list of drugs reimbursable under a health insurance plan; see DRUG LIST, NATIONAL DRUG LIST, POSITIVE LIST.

formulation Form under which a DRUG is presented as MEDICINAL PRODUCT; the f. is influenced by a number of factors such as the route of administration, chemical and biopharmaceutical properties of the substance (API); liquid f.s (especially aqueous solutions) can be administered by all routes but are bulky, more sensible to contamination and degradation and also more difficult to transport; if the drug is poorly soluble, suspensions (solid phase, i.e. particles distributed in liquid phase) or emulsions (two liquid phases, e.g. oil and water) may be produced; solid f.s appear most frequently as tablets which frequently contain a number of EXCIPIENTS (e.g. lactose, cellulose), followed by capsules, usually made by hard or soft gelatine; capsules enclose the drug as powder or non-aqueous liquid within their two halves; semi-solid f.s are e.g. creams (oil/water emulsions) or ointments (water/oil emulsions) used in topical preparations for treatment of skin or mucous membranes;

transdermal patches are applied like conventional sticking plasters and allow sustained drug release; COATING is also a factor that influences the properties of a tablet; see also ADJUVANT, ANTIOXIDANT, BYPRODUCTS, COMPONENT, CONTROLLED RELEASE FORM, DISINTEGRANTS, DOSAGE FORM, DRUG DELIVERY SYSTEMS, FILM COATING, HOT-MELT EXTRUSION, IMPURITY, LIPOSOME, NANOPARTICLES, PRESERVATIVES, PRODRUG, TABLET EXCIPIENTS.

fortified food see FUNCTIONAL FOOD, FOOD SUPPLEMENT.

forward-backward translation In order to ensure most accurate and comprehensive translation, e.g. for questionnaires, a first translator translates the text in the second language and a second translator back to the original language; discrepancies are then clarified; see also TEST-RETEST.

Framingham study A COHORT study that started in 1948 in a relatively small town (Framingham) in Massachusetts, U.S., and that is still ongoing, now including the third generation of subjects; the original objective was to study the development of cardio-vascular diseases in a large population (more than 5,000 men and women) that was not yet affected and to relate them to risk factors which have been identified as high blood pressure, smoking, high cholesterol, obesity, diabetes and physical inactivity being the most important; see also BIOBANK, COHORT STUDY, EVIDENCE-BASED MEDICINE.

fraud Intentional falsification of data in contrast to accidental ERROR; in science fraud occurs most often as trimming, (involves discard of DATA of the extremes so that they look cleaner or incorrect changes), cooking (ignoring/omitting certain data so that the rest will fit with the preconceived hypothesis) or outright fraud (fabrication of data); all these data may appear spurious when controlled by the MONITOR or DATA MANAGER; see also BLACK LIST, DATA DREDGING.

freezing of data base see DATA LOCK-POINT.

frequency of adverse reaction see ADVERSE REACTION, INCIDENCE PROPORTION.

functional food syn. nutraceutical; food, e.g., blueberry, broccoli, coffee, green tea, nuts, olive oil, salmon, saw palmetto, tomato concentrates or food rich in minerals such as whole grains (selen) or oysters (zinc) claimed to reduce the risk of cancer; the claimed effect is related to food components (bioactive compounds), e.g., to radical-scavengers such as polyphenols in fruits, genestein in soy extract, epigallocatechingallate in green and white tea, resveratrol in red wine and nuts, ß-caryophyllene as anti-inflammatory substance in origan, anti-inflammatory effects of chicken soup in upper respiratory tract infections, etc. that are supposed to provide a health benefit beyond basic nutrition ("HEALTH CLAIMS"); it is generally claimed that ff "rectifies" metabolic pathways and prevents, delays onset or delays

progression or even reverses diseases thus extending life beyond its normal time span; ff includes conventional food, fortified, enriched, or enhanced food; most differ functional food from DIETARY SUPPLEMENTS; see also ALIMENTARY RISKS, ALTERNATIVE MEDICINE, BIOACTIVE COMPOUNDS, FOOD SUPPLEMENT, MACROBIOTICS, NUTRIGENOMICS, ORTHOMOLECULAR MEDICINE, PHYTOMEDICINES, SELF-MEDICATION, TRADITIONAL HERBAL MEDICINAL PRODUCTS.

funnel plot graphical presentation of some measure of study precision plotted against effect size; a fp is used to investigate an eventual link between treatment effect and study size; see also FOREST PLOT.

futility Def. Inadequacy to produce a results or bring about a required end; etymology: futilis – that easily pours out, leaky, hence untrustworthy, vain, useless (Oxford Dictionary). Intervention has no pathophysiologic benefit; uncertain or controversial benefits; burdens/harms/costs outweigh the benefits; intervention has already failed in the patient, maximal treatment is failing.

G

gamma error syn. type III error; statistical risk of declaring a treatment better when in fact it is worse (truth: A > B, false judgment: A < B); usually negligible (for a = b = 0.05, then g < 1/10,000,000).

Gantt chart syn. bar chart; named after Henry L. Gantt who developed a graphic charting system to depict activities across a timescale; the chart displays each task as a bar, which shows the task's start and finish dates and duration on a time scale; see PROJECT MANAGEMENT.

Gaussian curve see DISTRIBUTION, STANDARD DEVIATION.

Gehan's design Useful for rejecting a drug (or hypotheses) from further study; usually there is no control group and the DESIGN can be kept unblinded when treatment results are objective resp. obvious; example: if with an antitumor DRUG no response occurs among the first 14 SUBJECTS, then the hypotheses of a response rate ≥20% can be rejected, accepting a false ERROR rate of 5 %; g.d. controls the probability of a false negative result by calculating the probability that the first n patients do not respond to the treatment for a pre-specified rate of response p to the drug; the initial sample size is determined as the smallest value of n such that the probability of n consecutive failures is less than some given error rate β; similar designs are: ECOG d., ONE SAMPLE MULTIPLE TESTING D.

gene A segment of chromosome that encodes the necessary regulatory and sequence information to direct the synthesis of a protein or RNA product; (e.g. Operator; Regulatory g.; Structural g.; Suppressor g; G. are instructions made of "base pairs" of nucleotides) that give organisms their characteristics; these instructions are stored in each cell of organisms in a long, string-like molecule, the DNA; within cells, the DNA is wound-up on themselves appearing as finite structures called chromosomes; each organism has his characteristic number of chromosomes, for humans the number is 46 (23 pairs); see also GENOME, PROTEOMICS.

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gene expression The process through which a gene is activated at particular time and place so that its functional product is produced; see also microRNA.

gene mapping Determination of the relative locations of genes on a chromosome.

gene sequencing Determination of the sequence of nucleotide bases in a strand of DNA.

gene silencing see RNA INTERFERENCE.

gene therapy syn. genomics therapy; the replacement of a defective gene in an organism suffering from a GENETIC DISEASE; more general: techniques inducing immunological reactions by the transfer of new genetic material into human cells for the purpose of treating, preventing or diagnosing a disease; recombinant DNA techniques are used to isolate the functioning gene and insert it into cells e.g. by delivering genes via an artificially altered virus such as herpesviruses, lentiviruses or RETROVIRUSES, the DISC virus (disabled infectious single cycle viral vector), or AAV (adeno-associated virus), e.g. in case of patients with cystic fibrosis, which functions as vector, containing a functioning copy of the gene to correct that defect, or that stimulate the immune system to combat diseases such as cancer (defective p53 gene in about 50 % of cancers) or chronic/persisting virus infections; instead of adding a gene to a cell, inhibiting gene expression may be an alternative; over 300 single gene genetic disorders have been identified in humans, a significant percentage of these may be amenable to gene therapy; see also ADVANCED THERAPY, ANTISENSE OLIGONUCLEOTIDES, BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, BIOTECHNOLOGY, CLONING, ETHNIC DIFFERENCES, GENOMICS, IMMUNOTHERAPY, METABOLISM, PHARMACOGENETICS, RIBOZYME, TRANSGENIC DRUG.

genetic disease Disease linked to a genetic variance or genetic defect such as a mutated gene; there are about 4,000–5,000 genetic diseases known to medical science such as cystic fibrosis, Down syndrome, sickle cell anaemia, haemophilia, Gilles de la Tourette syndrome or Fabry's disease; furthermore, some 240 cancer-related genes have been discovered so far; see also GENE THERAPY, GENETIC VARIANCE, ORPHAN DISEASES.

genetic polymorphism Genetic diversity that causes inter-individual differences in susceptibility to clinical diseases, but also to drug treatments, e.g. due to differences in the METABOLISM; see also GENE, GENOME.

general sale list medicine (GSL) Drug which may be sold at any shop without supervision from a pharmacist or a doctor (UK); see also CONTROLLED DRUG, GRAS-LIST, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE.

generic Often used as short term for GENERIC MEDICINAL PRODUCT; a DRUG containing the same active ingredient as a drug already approved and which is

interchangeable with the original product which is no longer covered by patents or other legal regulations; opp. PROPRIETARY MEDICINAL PRODUCT; see also BIOSIMILAR, ESSENTIALLY SIMILAR PRODUCT.

generic application EMA: "application for a product ESSENTIALLY SIMILAR to a so called reference product; the applicant is not requested to provide the results of toxicological and pharmacological tests or of clinical trials"; can only be placed on the market 10 (11) years after the authorization of the reference medicinal product; a g.a. can also be submitted in a member state of the EC where the reference medicinal product has never been authorized; see also ABBREVIATED NEW DRUG APPLICATION, ACCELERATED APPROVAL PROGRAM, APPLICATION, BIBLIOGRAPHICAL APPLICATION, INFORMED CONSENT APPLICATION, MUTUAL RECOGNITION PROCEDURE.

generic medicinal product A medicinal product which has (i) the same qualitative and quantitative composition in active substance(s) as the reference product; (ii) the same pharmaceutical form; (iii) whose bioequivalence with the reference medicinal product has been demonstrated; different salts or derivates shall beconsidered to be the same active substance; frequently it is marketed under the non-proprietary (generic) name of the drug; see also BIOEQUIVALENCE, GENERIC APPLICATION.

generic name syn. INTERNATIONAL NON-PROPRIETARY NAME; opp. (registered) trade mark, TRADE NAME, BRAND NAME.

genetic code The mechanism by which genetic information is stored in living organisms. The code uses sets of three nucleotide bases (codons) to make the amino aids that, in turn, constitute proteins.

genetic engineering syn. recombinant DNA technology, biotechnology; a technology used to alter the genetic material of living cells in order to make them capable of producing new substances or performing new functions; in the "genetically modified organism" (GMO) the genetic information (DNA) is changed such that it does not occur naturally; this procedure is highly "mutagenic"; a number of health risks have been associated with GM food (immune dysregulation, accelerated aging, infertility etc.); see ALIMENTARY RISKS, BIOTECHNOLOGY, PLASMID.

genetic polymorphism Variability of the genetic information related to the cytochrom P450 enzyme complex of the liver which is responsible for many forms of drug metabolisations; see also GENETIC DISEASE, GENETIC VARIANCE, GENOTYPE, INTERACTION OF DRUGS.

genetic variance Variability of the genetic information (alleles) due to different genomic positions, single nucleotide polymorphisms, indels, copy number

variants (CNVs) and inversions, allele frequencies (rare, low-frequency and common) and effect sizes; g.v. may for instance explain the individual risk for diseases or increased/decreased metabolisation of drugs (genetic polymorphism); see also ALLELE, GENE, GENETIC DISEASE, GENOME, GENOTYPE, INTERACTION OF DRUGS, METABOLISM, PERSONALISED MEDICINE, PHENOTYPE, PROTEOMICS.

genie score SCORE constructed with laboratory DATA which belong to a functional group (i.e. values that are related to a particular body function, e.g. SGOT, SGPT, LDH, alkaline phosphate, bilirubin are indicative of liver function); g.s. are used to study laboratory abnormality profiles of drugs for assessments of SAFETY; g.s. from different body functions can also be combined to produce an overall abnormality INDEX; see also COMPOSITE VARIABLE.

genome The total hereditary material of a cell, comprising the entire chromosomal set found in each nucleus of a given species; the human g. has approximately 2.9 billion bases corresponding to approx. 25,500 genes, 20,500 of which encode for proteins; the genomes of human and chimpanzees are 98.5 % identical, roundworms have only about 1,000 genes less; human individuals share on average 99.7–99.9 % of their genetic identity; a large part in making one human being genetically different from another is due to single nucleotide polymorphisms (SNPs); it is estimated that approximately 750,000 SNPs exist; they account for variations such as height or eye colour but determine also the patients response to pharmaceutical intervention; about 80 % of the human genome has "regulatory" functions, only 2 % f codes for proteins; these human genes can produce over 100,000 functionally different proteins whereby post-translational modifications of proteins have an important role; see also ALLELE, DRUGGABLE GENOME, GENE, GENOMICS, PERSONALISED MEDICINE, PROTEOMICS.

genomics Science that studies the genomes (i.e., the complete genetic information) of living beings. This commonly entails the analysis of DNA sequence data and the identification of genes; used for identifying genes which can be linked to a particular disease; human cells have approximately 25,000 genes of which more than 60 have been linked to diseases up to now; see also GENE THERAPY.

genomics therapy see GENE THERAPY, PROTEOMICS.

genotoxicity Toxic effects upon genetic material (DNA) of cells, inducing permanent and transmissible damages in the amount and/or structure of the DNA (chromosomes); changes can occur as: point mutations (with changes – substitution, addition or deletion – in one or a few base pairs within a gene), as chromosomal mutations (with microscopically detectable structural alterations) or as genomic mutations (numerical aberrations with changes – gain or loss – of chromosomes); see also ANEUGEN, CLASTOGEN, MICRONUCLEUS TEST, MUTAGENICITY TEST, TOXICITY TESTS.

genotype Entire genetic make-up (configuration) of an individual or group; (the PHENOTYPE is the actual expressed traits or characteristics found within an organism); the distinction between genotype and phenotype can be made based on DOMINANT and RECESSIVE genes; a dominant gene is an expressed characteristic trait within an organism, where as a recessive trait is not (example: human blood types, AB are co-dominant); see also ALLELE, GENE, GENETIC POLYMORPHISM, GENOME, METABOLISM, PROTEOMICS.

geriatric evaluations (GCP) Elderly people (above 65 years) are often classified according to age: 66–75 "young-old", 76–85 "middle-old" and > 85 "old-old" or "oldest old"; regulations concerning licensing of drugs for elderly people frequently request specific pharmacokinetic testing, adequate labelling, maintenance of a representative database, and reasonable numbers of patients included in PHASE III trials as a minimum; see also VOLUME OF DISTRIBUTION.

geriatric population ICH: "patients aged 65 years or older"; "… the geriatric p. should be represented sufficiently to permit the comparison of drug response in them to that of younger patients; for drugs used in diseases not unique to, but present in, the elderly a minimum of 100 patients would usually allow detection of clinically important differences"; in 2003, the population 65+ represents between 12.4 % (US) and 18.6 % of the overall population in industrialized countries and may progress to 18.2 and 28.0 % in 2025; annual pharmaceutical expenditure for the population 65+ is about 2.5 times higher than for non-seniors; see also COMPLIANCE, PRESCRIPTION.

glidants see EXCIPIENTS.

global assessment variable Variable to measure overall efficacy or tolerance e.g., symptom severity; it integrates overall impression about the state and change of the state of a subject; usually a scale of ordered categorical ratings that have some subjective component; example: CGI – Clinical Global Impression scale; see also COMPOSITE VARIABLE, GENIE SCORE.

glomerular filtration rate (GFR) Glomerular membranes of the kidney filtrate about 130 ml of plasma/min or 190 L/day; about 1.8 L of this volume is excreted as urine, the remainder reabsorbed in the renal tubules; it can be calculated by the formula of Jelliffe (Ann Int Med 79:604–605, 1973); GFR = (98 − 0.8 (age − 20)) × body surface area/(serum creatinine × 1.73); the result is to be multiplied with 0.9 for females and 1.0 for males; see also CREATININE CLEARANCE, EXCRETION.

good clinical practice (GCP) syn. good clinical regulatory practice, good clinical research practice, good clinical trial practice; EC (III): "A standard by which CLINICAL TRIALS are designed, implemented and reported so that there is public

assurance that the DATA are credible, and that the rights, integrity and CONFIDENTIALITY of SUBJECTS are protected"; FDA does not give an official definition of GCP; within the EC the guidelines for GCP came into force 1 July 1991 and are mandatory for the member states since 1 January 1992; the two cornerstones of GCP are (i) protection of the subjects and (ii) reliability of data and conclusions; the WHO has also issued "Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products" in February 1994; they have been superseded in May 1996 by the ICH E6 Guideline for Good Clinical Practice, mandatory in the three ICH regions (Japan, Europe, United States) since January 1997; see also GOOD CLINICAL TRIAL PRACTICE, INTERNATIONAL CONFERENCE ON HARMONISATION (ICH).

good clinical regulatory practice (GCRP) syn. GOOD CLINICAL PRACTICE; term used by Australian health authorities.

good clinical research practice (GCRP) syn. GOOD CLINICAL PRACTICE; term used in UK.

good clinical trial practice (GCTP) syn. GOOD CLINICAL PRACTICE, term used by the Nordic Guidelines, prepared by the Nordic Council on Medicines in collaboration with the drug regulatory authorities of Denmark, Finland, Iceland, Norway and Sweden (first edition 1989).

good laboratory practice (GLP) Standards for laboratory investigations; GLP principles are defined by the EC (I) as: "principles of good laboratory practice, that are consistent with the OECD principles of good laboratory practice as adopted in article one of directive 87/18/EEC".

good manufacturing practice (GMP) EC (IV): "The part of the pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use and as required by the product specification"; the FDA had 269 recalls in 1994, 248 in 1993, and 339 in 1992 for quality problems; according to the FDA, a firm must have the following records required by their GMP regulations: DEVICE MASTER RECORDS, device history records, maintenance schedules and records, complaint files/failed device or component files, AUDIT reports, distribution records, personnel training records; see also <www.recalls.gov>, HYGIENE PROGRAM, ISO 9000, PRODUCT RECALL, QUALIFIED PERSON, also PRODUCT QUALITY REVIEW, REFERENCE SAMPLE, RETENTION SAMPLE, SITE MASTER FILE.

good pharmacovigilance practice (GVP or GPvP) see PHARMACOVIGILANCE.

good postmarketing surveillance practice (GPMSP) In some countries (e.g. Japan) guidelines for monitoring prescription drugs, NEW CHEMICAL ENTITIES, new indications, combinations of drugs, routes of administration, dosages a.s.o. exist, which make it necessary for companies to establish a dedicated

POSTMARKETING SURVEILLANCE management department, appoint suitable educated and trained staff, and designate a manager responsible for forwarding relevant information to the national health authority; see also SURVEILLANCE.

good regulatory practice (GRP) Standards for regulatory practices.

GP trial see MEDICAL OFFICE TRIAL.

G protein coupled receptors (GPCRs) proteins located at the interface between the interior and exterior of cells that have a key role in signalling (second messenger pathways); they are potential drug targets as many drugs act at least partially via GPCRs, e.g., dronabinol via cannabinoid receptor 1 (CB1) and 2 (CB2); others are morphine, mescaline or adrenaline; up to now, about 390 GPCRs have been identified; see also ENDOCANNABINOIDS.

G-grade see TNM-STAGING.

Graeco-Latin square Special CROSS-OVER DESIGN; employs both Latin and Greek letters and allows, in comparison with the LATIN SQUARE D., equalisation of variations for an additional source of variation, e.g. for the administration route; e.g. three groups receive sequentially three treatments A, B, C, administered orally (alpha), intramuscularly (beta) and intravenously (gamma); then group 1 receives Aα, Bβ, Cγ, group 2 Bγ, Cα, Aβ and group 3 Cβ, Aγ, Bα.

GRADE Guidelines for the synthesis and grading of evidence and for the performance of health technology assessments (www.gradeworkinggroup.org/).

GRAS-list List of drugs "generally regarded as safe" by the FDA; these substances are permitted to be manufactured and sold OVER-THE-COUNTER without prior FDA approval; see also CONTROLLED DRUG, GENERAL SALE LIST MEDICINES, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE.

Gross Domestic Product (GDP) Final consumption + gross capital formation + net exports; actual final consumption of households includes those goods and services used by households or the community in order to satisfy their individual wants and social needs. (Actual final consumption expenditure includes final consumption expenditure of households, general government and non-profit institutions serving households.)

group-randomized controlled clinical trial see CLUSTER RANDOMISED CONTROLLED CLINICAL TRIAL, DESIGN.

guidance syn. guideline, note for guidance; see EC LAW.

guide syn. guideline, note for guidance; see EC LAW.

guideline syn. guide, note for guidance; term used for documents which are not legally binding, in contrast to a DIRECTIVE; represents the agency's (e.g., EC, FDA) current thinking; an alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations or both; see DIRECTIVE, EC LAW, REGULATION.

GXP Acronym for commonly accepted quality standards for any practice (e.g., GOOD CLINICAL PRACTICE, GOOD LABORATORY PRACTICE, GOOD MANUFACTURING PRACTICE etc.).

H

half life (t1/2) Time within which half of a substance has been eliminated from the body (time taken for plasma concentrations to fall by 50 %); see CLEARANCE, ELIMINATION, KINETIC, PHARMACOKINETIC, TREATMENT SCHEDULE.

harm Damage to health, including the damage that can occur from loss of product quality or availability; see also HAZARD.

harmonised standard European Norm (EN) that has been accepted by all member states and published in the Official Journal of the EC.

handicap WHO: "a disadvantage for a given individual resulting from an IMPAIRMENT or a DISABILITY, that limits or prevents the fulfilment of a role that is normal for that individual"; see also DISABILITY, DISEASE, HEALTH, ILLNESS, IMPAIRMENT.

Harmonised Birth Date (HBD) Virtual date of first marketing authorisation in a EC member state ("birth date") aimed to harmonise the PERIODIC SAFETY UPDATE REPORT (PSUR) submission schedules of medicinal products containing the same active substance; see also DATA LOCK POINT, EUROPEAN UNION REFERENCE DATE, INTERNATIONAL BIRTH DATE.

Havard style of citation Style of CITATIONS in scientific journals; references should be listed in alphabetical order and then by year. For example: (i) Fazekas, F., Deisenhammer, F., Strasser-Fuchs, S., Nahler, G., Mamoli, B. for the Austrian Immunoglobulin in Multiple Sclerosis Study Group. (1997) Randomised Placebo-Controlled Trial of Monthly Intravenous Immunoglobulin Therapy in Relapsing-Remitting Multiple Sclerosis, Lancet 349: 589–593. (ii) Nahler, G. (1994) Dictionary of Pharmaceutical Medicine, Springer Publishing Co., Wien, New York, Austria. (iii) Nahler, G. (1996) "International Medical Device Registration. Austria" Donawa M.E., eds., pp. 33–58, Interpharm Press, Buffalo Grove, IL. (iv) USP XVI

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(1960) The United States Pharmacopoeia, pp. 817–819, Mack Publishing Co., Easton, P.A. See also VANCOUVER STYLE.

Hawthorne effect Study participation per se affects the outcome (it makes patients to feel "important", thus producing a psychological stimulus and a better outcome); especially behavioural measures are subject to this effect (e.g., Alzheimer's Disease Assessment Scale – ADAS). The Hawthorne Effect was first reported following a research programme investigating methods of increasing productivity in the Western Electrical Company's Hawthorne Works in Chicago during the 1920s and 1930s. The finding of enduring interest was that no matter what change was introduced to working conditions, the result was increased productivity. For example, improving or reducing the lighting in the production areas under test produced similar effects. Subsequently the definition has been broadened; in clinical research it refers to treatment response; see also BIAS, LABELLING PHENOMENON, PLACEBO EFFECT, WHITE-COAT HYPERTENSION.

hazard The potential source of harm (ISO/IEC Guide 51); see also HARM.

hazard ratio Ratio of expected MEDIANS of time-to-event distributions in the two treatment arms when these DATA follow an exponential distribution.

healing Elimination of an abnormal condition either with or without (medical) intervention; see also CURE.

health WHO: "a state of complete physical, mental and social well-being and not merely the absence of DISEASE or infirmity"; see also DISABILITY, DISEASE, HANDICAP, ILLNESS, IMPAIRMENTS.

health care expenditure The total expenditure on health measures, the final consumption of health goods and services (i.e. current health expenditure) plus capital investment in health care infrastructure. This includes spending by both public and private sources (including households) on medical services and goods, public health and prevention programmes and administration. Excluded are health-related expenditure such as training, research and environmental health. The two major components of total current health expenditure are: expenditure on personal health care and expenditure on collective services. The health expenditure per capita, public and private, increases (US $, OECD, Health at a glance, http://www.oecd.org) 2007 vs 2009: Austria 3,519 vs 4,289, France 3,374 vs 3,978, Germany 3,287 vs 4,218, Italy 2,532 vs 3,137, Japan 2,358 vs 2,878, Norway 4,364 vs 5,352, Spain 2,331 vs 3,067, Switzerland 4,177 vs 5,144, UK 2,724 vs 3,487, US 6,401 vs 7,960; the health expenditure as a share of the GROSS DOMESTIC PRODUCT, was (in % of GDP, OECD, Health at a glance 2007): Austria 10.2 %, France 11.1, Germany 10.7, Italy 8.9, Japan 8.0, Norway 9.1, Spain 8.2, Switzerland 11.6, UK 8.3, US

15.3 %; in western countries about 35–50 % of these costs are expended for the ELDERLY; in 2000, about 1.4 % of the GDP of the EU have been expended for pharmaceutical, and costs for pharmaceuticals have represented about 16 % of overall costs for health care; see also DRUG CONSUMPTION, ECONOMIC ANALYSES, HEALTH CARE SERVICES, MEDICAL CULTURE, PHARMACEUTICAL EXPENDITURE, PRICE REGULATORY SCHEME, PRESCRIPTION.

health care services Densities of doctors per inhabitants vary widely, e.g. 1/248 in Austria, 1/293 in Germany, 1/299 in Belgium, 1/328 in France, 1/420 in The Netherlands and 1/472 in the US (figures of 1995–1996); densities of beds per population of 1,000 inhabitants vary between 3.8 (USA), 4.1 (Netherlands, Sweden), 5.3 (France), 6.3 (Switzerland), 6.8 (Austria) and 7.3 (Germany; figures of 1989); see also MEDICAL CULTURE.

health claims Claims made in commercial communications concerning foods as having a nutritional, physiological or other health advantage over similar or other products to which such nutrients and other substances are not added; claims are authorised only after harmonised scientific assessment of such claims by the European Food Safety Authority (Regulation (EC) No 1924/2006); see FOOD SUPPLEMENT, FUNCTIONAL FOOD.

health emergency see PUBLIC HEALTH EMERGENCY.

health expenditures see HEALTH CARE COSTS.

health profile Instrument for measuring QUALITY OF LIFE, often overlapping with QUALITY OF LIFE SCALE, WELL-BEING SCALE; health profiles are designed for a wide variety of conditions and can be used to compare the effects of interventions in different DISEASES; examples for h.p.s are: Sickness Impact Profile, McMaster Health Index, Nottingham Health Profile, Hamilton's rating scale for anxiety states, Taylor's Manifest Anxiety Scale, Eysenck Personality Inventory (measuring whether or not a SUBJECT has a neurotic personality), a.s.o.

health-related quality of life (HRQOL) Narrower term than QUALITY OF LIFE; it includes that well being of a patient is influenced also by factors unrelated to DISEASE or treatment e.g. education, environment a.s.o.

Health Technology Assessment (HTA) bodies – Bodies that assess innovations in medical care in terms of their clinical performance and cost-effectiveness and provide decision-makers with evidence-based tools for prioritising healthcare treatments in terms of their utility, efficiency and cost-effectiveness; some can be regulatory: they are accountable to health ministers and are responsible for listing and pricing drugs, medical devices and other related services (e.g. Finland, France, Sweden, UK); examples for national HTA bodies: National Institute for

Health and Clinical Excellence (NICE), UK or the Institute for Quality and Efficiency in Health Care (IQWiG), Germany.

health utilities index (HUI) Index for classification of the health status of an individual; attributes to this index are: seeing, hearing, speaking, walking, use of fingers and hands, feelings, memory and thinking, and pain and discomfort; see also QUALITY OF LIFE.

healthy-year equivalent (HYE) see QUALITY ADJUSTED LIFE YEAR.

Heaton–Ward effect Subjective assessments can be severely biased by violation of blinding or the expectation of the observer: in a supposed cross-over trial the observer is likely to report a deterioration after cross-over if he initially assumed an improvement and an improvement in those he first imagined had not occurred; see also BIAS, BLINDING, DESIGN.

heart insufficiency score see NEW YORK HEART ASSOCIATION.

Helsinki declaration see DECLARATION OF HELSINKI.

herbal drug see HERBAL SUBSTANCE; see also HERBAL MEDICINES, HERBAL MEDICINAL PRODUCT, HERBAL PREPARATIONS, PHYTOCHEMICAL, PHYTOMEDICINE, PHYTONUTRIENT, TRADITIONAL HERBAL MEDICINAL PRODUCT.

herbal medicinal product "Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations" (Dir 2001/83/EC); within the EC, (non-binding) "Community Herbal Monographs" and a (binding) "Community List of Herbal Substances, Preparations and Combinations" exist; for herbal medicines listed in the Community List the applicant is not required to provide evidence of the safe and traditional use, and authorities cannot request additional data; see also HERBAL MEDICINES.

herbal medicines syn. natural remedies, phytomedicine; see HERBAL MEDICINAL PRODUCT, HERBAL PREPARATIONS, HERBAL SUBSTANCES, NAMING CONVENTION, PHYTOMEDICINES, TRADITIONAL HERBAL MEDICINAL PRODUCT, WELL-ESTABLISHED MEDICINAL USE.

herbal substances syn. herbal drug; "Any mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)" (Dir 2001/83/EC); see HERBAL MEDICINES.

herbal preparations "Preparations obtained by subjecting herbal substances to treatment such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates" (Dir 2001/83/EC); see HERBAL MEDICINES.

hereditary disease see GENETIC DISEASES, ORPHAN DISEASES.

heterocygote Different alleles for a specific GENE; see also ALLELE, DOMINANTE, HOMOCYGOTE, RECESSIVE.

high level term (HLT) see medDRA, WHO ADVERSE REACTION TERMINOLOGY.

high-tech medicinal products EC (I): "A): medicinal products developed by means of the following biotechnological processes: (1) recombinant DNA technology, (2) controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, (3) hybridoma and monoclonal antibody methods; B): other high-technology medicinal products: (1) other biotechnological processes which, in the opinion of the competent authority concerned, constitute a significant innovation, (2) medicinal products ad-ministered by means of new delivery systems which, in the opinion of the competent authority concerned, constitute a significant innovation, (3) medicinal products containing a new substance or an entirely new indication which, in the opinion of the competent authority concerned, is of significant therapeutic interest, (4) new medicinal products based on radio-isotopes which, in the opinion of the competent authority concerned, are of significant therapeutic interest, (5) medicinal products the manufacture of which employs processes which, in the opinion of the competent authority concerned, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity"; see also CENTRALISED PROCEDURE.

high-tech procedure see CENTRALISED PROCEDURE.

historical control Group of patients who had received – often within the same organisation – a standard treatment in the past and with which a new treatment is compared; in LITERATURE CONTROLS this group is made up of patients treated elsewhere and previously reported in the medical literature; conclusions made from comparisons with h.c. however may be subject to severe BIAS due to differences in patient selection, diagnostic techniques, environmental conditions a.s.o.; see also BIAS, CONTROL, MATCHED PAIRS, MINIMIZATION.

Hochberg correction In order to avoid ERRORS by repeated significance testing the SIGNIFICANCE LEVEL is divided by the number of comparisons; see also BONFERRONI CORRECTION.

home based CRA see CLINICAL RESEARCH ASSOCIATE.

homeopathy Def. (WHO) "A therapeutic system which works on the principle that 'like treats like'. An illness is treated with a medicine which could produce similar symptoms in a healthy person. The active ingredients are given in highly diluted form to avoid toxicity"; homeopathic remedies are virtually 100 % safe; see also ALLOPATHY.

homocygote Identical alleles for a given GENE; see also ALLELE, DOMINANTE, HETEROCYGOTE, RECESSIVE.

hospital file see PATIENT FILE.

hot-melt extrusion (HME) Technological process whereby a new material (the extrudate) is formed by forcing it through an orifice under controlled conditions; applied to pharmaceutical manufacturing it improves dissolution rates of poorly water-soluble drugs by making a solid dispersion in a polymer matrix whereby a large variety of dosage forms and formulations such as granules, pellets, tablets, controlled-release devices, implants, transdermal systems and ophthalmic inserts can be produced; widely used in food, rubber and plastic industry; see also FORMULATION.

Huriet see LOI HURIET.

hybrid procedure Submission of additional documentation in the form of certain pharmacological or toxicological tests or clinical trials by an applicant in order to demonstrate that his product is "essentially similar" to the reference product does not preclude an ABRIDGED APPLICATION procedure; see also APPLICATION, BIBLIOGRAPHIC APPLICATION.

Hygiene program Procedures relating to health, hygiene and clothing of personnel during manufacturing; see GOOD MANUFACTURING PRACTICE, LOI HURIET.

ICD-9 code International Classification of Diseases, 9th edition; see CODE.

ICD-10 code International Classification of Diseases, 10th edition; (free access: http://www.dimdi.de); see CODE.

ideal body weight see LORENTZ FORMULA.

identified see CODE.

idiosyncratic reaction Non-immunological hypersensitivity reaction to a substance, also called reactive metabolite syndrome; adverse reaction to a drug that is not dose-dependent, has a variable time of onset and is usually unpredictable (type B-reaction); example: malignant hyperthermia after anaesthesia; it is assumed that idiosyncratic reactions result from the imbalance between the formation of a toxic metabolite and it's detoxification that may be genetically determined; see also ADVERSE REACTION, IMMUNOLOGIC REACTION, PHARMACOGENETICS.

IEEE Standard 1062–1993 Standard on the "Recommended practice for software acquisition", published by the Institute of Electrical and Electronic Engineers; see also INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, ISO STANDARD 9000–3.

IFAPP see INTERNATIONAL FEDERATION OF PHARMACEUTICAL PHYSICIANS.

IFPMA see INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATION.

IFPMA code of pharmaceutical marketing practices Voluntary and self-limiting regulations of the IFPMA member companies; principles of this code are e.g. that "no public communication shall be made with the intent of promoting a pharmaceutical product as safe and effective for any use before the required approval of the pharmaceutical product for marketing

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for such use is obtained"; "statements in promotional communications should be based upon substantial scientific evidence or other responsible medical opinion"; "promotional communications should have medical clearance or, where appropriate, clearance by the responsible pharmacist, before their release"; see also CODE OF PRACTICE.

illness Subjective feeling of not feeling well or normal; i. can be considered at four different levels: DISABILITY, IMPAIRMENT, HANDICAP and pathology; see also DISEASE, HEALTH.

immediate release form (IR) opposite: DELAYED RELEASE form; see also CONTROLLED RELEASE FORM, FORMULATION, PROLONGED RELEASE.

Immediately reportable adverse event see ADVERSE EVENT OF SPECIAL INTEREST.

immortal time bias Bias that may arise particularly in pharmacoepidemiological studies when the period between entry in the COHORT and date of first exposure (e.g., to a drug) during which death has not occurred, is not accounted for in the analysis or excluded; see BIAS.

immunologic reaction Examples of i.reactions.: Type I (IgE-mediated, minutes to hours after exposure): anaphylaxis, urticaria, bronchospasm; type II (cytotoxic): haemolytic anaemia, neutropenia; type III (immune complex reaction, 1–3 weeks after exposure): serum sickness, fever, urticaria, vasculitis; type IV (cell-mediated, delayed type, 2–7 days after cutaneous exposure): contact dermatitis, maculopapular rash; other forms of immunologic reactions are specific T-cell activation: morbiliform rash or Fas/Fas ligand-induced apoptosis: Stevens-Johnson syndrome; non-immunologic reactions are e.g., idiosyncratic reactions or drug-drug interactions; see also ADVERSE DRUG REACTION, DRUG INJURY, IDIOSYNCRATIC REACTION, SPONTANEOUS ADVERSE DRUG REACTION REPORT.

immune system The aggregation of cells, biological substances (such as antibodies), and cellular activities that work together to provide resistance to disease; see also BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, BIOTECHNOLOGY, GENE THERAPY.

immunity Non-susceptibility to a disease or to the toxic effects of antigenic material; active immunity is when the organism produces antibodies against a specific agent e.g. by exposition (natural acquired a.i.) or vaccination (artificially acquired a.i.); a.i. is long lasting or even permanent in contrast to passive immunity is short-term immunization usually by the injection of antibodies, such as gamma globulin, that are not produced by the recipient's cells. Naturally acquired passive immunity occurs during pregnancy, in which certain antibodies

are passed from the maternal into the foetal bloodstream; cell-mediated immunity is an immune response that does not involve antibodies or complement but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen; humoral immunity is mediated by secreted antibodies (as opposed to cell-mediated immunity which involves T lymphocytes) produced in the cells of the B lymphocyte lineage (B cell). Secreted antibodies bind to antigens on the surfaces of invading microbes (such as viruses or bacteria), which flags them for destruction.

immunology Study of all phenomena related the body's response to antigenic challenge (i.e., immunity, sensitivity, and allergy).

immunmodulators A diverse class of proteins that boost the IMMUNE SYSTEM. Many are cell growth factors that accelerate the production of specific cells that are important in mounting an immune response in the body. These proteins are being investigated for use in possible cures for cancer.

immunotherapy Techniques inducing immunological reactions for therapeutic purposes; (e.g. by delivering genes via an artificially altered virus such as the disabled infectious single cycle viral vector or DISC virus) that stimulate the immune system to combat diseases such as cancer or chronic/persisting virus infections; see also BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, BIOTECHNOLOGY, GENE THERAPY.

immunotoxicity Substances can have untoward effects on the immune system; experimental models used to investigate such effects are e.g. macrophagic cytolytic activity, occluded batch tests, lymphocyte proliferative response to mitogens, mixed lymphocyte reaction, delayed type hypersensitivity, a.s.o.; see also TOXICITY.

impact factor of journals The journal impact factor is the most widely cited bibliometric tool used to characterise journals. It was originally proposed 50 years ago as a measure of the impact that individual articles have on the research community, but it is now more commonly used across all articles published by a journal to provide a measure of a journal's impact on the research community rather than the impact of an individual article. The journal impact factor is thus calculated as the number of citations a journal has received in the last complete year for articles published in the two preceding years, divided by the total number of articles the journal published in the two preceding years. So it gives an average number of citations of published articles, without giving any unfair advantage to the larger or more frequently published journals. Such journal citation reports are used widely as the basis for assessing research output. They are used by funding bodies to gauge the quality of publications, by

researchers to assess which journals they choose to submit manuscripts to, and as a basis for journals to attract new subscriptions and advertising.

impairments WHO: "abnormalities of body structure and appearance and organ or system function, resulting from any cause"; includes e.g. loss of limbs, limitations in range of motion, mental i. a.s.o.; see also DISABILITY, DISEASE, HANDICAP, HEALTH, ILLNESS.

impurity I. in drug products can be classified as DEGRADATION PRODUCTS of the ACTIVE INGREDIENT, reaction products of the active ingredient with an excipient and/or immediate container/closure system; all I. present below ≤0.1 % do not need to be qualified except if they are particularly toxic (metal impurities are dealed with in ICH Q3D); i. may be, among others, related to directly to the synthesis (e.g. residues from previous steps of synthesis, originating from raw materials or solvents), to the formulation (e.g. EXCIPIENTS) or to the environment (light, temperature, humidity) or container system (e.g., glass particles); I. that appear only sporadically have to be included in the profile as well; see also CLIMATIC ZONES, CONTAMINATION, FORMULATION, STABILITY TEST.

imputabilty see CAUSALITY.

IMRAD Common structure for REPORTS (introduction, material/methods, results, analysis of results, discussion).

incapacitated subjects see VULNERABLE SUBJECT.

incidence proportion syn. relative incidence; def.: number of SUBJECTS who, over a specific time, develop a specific attribute (adverse reaction)/total number of subjects exposed; definitions based on ICH: very common >10 %, common 1–10 %, uncommon 0.1–1 %, rare 0.01–0.1 %, very rare <0.01 %; acute < 1 h, sub-acute <1 day, latent > 1 day; see also AGE-SPECIFIC RATE, ATTACK RATE, CLUSTERS, CUMULATIVE INCIDENCE, EXCESS INCIDENCE, PREVALENCE RATE.

incidence rate def.: number of SUBJECTS who, over a specific time, develop a specific attribute/ total number of subjects at risk (person-years), or patient-time or equivalent units (courses of treatment, prescriptions, patient-months, etc.) e.g. number of new cases of a disease per year; see also AGE-SPECIFIC RATE, ATTACK RATE, CLUSTERS, CUMULATIVE INCIDENCE, EXCESS INCIDENCE, INCIDENCE PROPORTION, PREVALENCE RATE.

incident see MEDICAL DEVICE REPORTING.

included term see WHO ADVERSE REACTION TERMINOLOGY.

inclusion criteria Criteria defining a DISEASE (stage, group of subjects) as close as possible; i.c. and EXCLUSION C. form the entry criteria (ELIGIBILITY C.) of a CLINICAL TRIAL.

inclusion period see RECRUITMENT PERIOD.

incubation period Time between exposure to an infectious agent and development of clinical signs and symptoms of infection; see also LATENT PERIOD, SECONDARY ATTACK RATE.

IND safety report FDA: "The SPONSOR shall notify FDA and all participating investigators in a written INVESTIGATIONAL NEW DRUG (IND) s.r. of any ADVERSE EXPERIENCE associated with use of the DRUG that is both serious and unexpected. Such notification shall be made as soon as possible and in no event later than ten working days after the sponsor's initial receipt of the information… The sponsor shall also notify the FDA by telephone of any unexpected fatal or LIFE THREATENING experience associated with the use of the drug in the clinical studies conducted under the IND no later than three working days (five for trials conducted outside the US) after receipt of the information …"; see also INVESTIGATIONAL DRUG.

indemnification Insurance provided by a SPONSOR to an INVESTIGATOR to cover the costs which may arise from a law suit carried on by a patient; acts of negligence however would only be covered by the medical insurance of the investigator; see also COMPENSATION FOR DRUG INDUCED INJURY, INSURANCE, PRODUCT LIABILITY.

independent ethics committee (IEC) see ETHICS COMMITTEE.

index Inventory providing a single number to characterise a set of item responses by a simple cumulative SCORE; see also SCALE.

index patient The first affected family member through whom the family was first identified; see also EMPIRIC RECURRENCE RISK, INCIDENCE RATE.

indirect treatment comparisons (ITC) In the absence of trials involving a direct comparison of treatments of interest, an indirect comparison can be provide useful evidence of the difference in treatment effects among competing interventions (which otherwise would be lacking) and for judiciously selecting the best choice(s) of treatment; example: if two particular treatments have never been compared against each other, head to head, but these two treatments have been compared to a common comparator, then an indirect treatment comparison can use the relative effects of the two treatments versus the common comparator; see also BRIDGING.

individual case safety report (ICSR) a notification from a health professional regarding a patient with a disorder that is suspected to be drug-related; medically unconfirmed ICSRs are provided as a line listing annexed to the PSUR; an ICSR may origin from a clinical trial or spontaneously from a marketed drug (equivalent to: expedited adverse reaction report); for centrally authorised

medicinal products periodic ICSRs should be transmitted; since 2012, EMA operates a public and searchable "EUROPEAN DATABASE OF SUSPECTED ADVERSE REACTION REPORTS" (http://www.adrreports.eu/); see also ADVERSE REACTION, CONSUMER REPORT, DRUG-EVENT COMBINATION, EUDRA VIGILANCE, EXPEDITED REPORTING, ISO COUNTRY CODE, MASTER CASE, PERIODIC SAFETY UPDATE REPORT.

inevaluability rate syn. disqualification rate; as a rule of thumb, the percentage of patients considered inevaluable for response or other primary endpoint due to missing DATA, PROTOCOL violations, loss to follow-up a.s.o. should not exceed 15–20 %; higher figures reflect poor monitoring, poor study conduct and/or inappropriate patient selection or evaluation criteria; results are in general not sufficiently reliable, when the i.r. approaches the magnitude of the difference in outcomes being tested; see also DROP-OUT, INTENT-TO-TREAT ANALYSIS, WITHDRAWAL.

infants Children aged 0–28 days; see AGE GROUPS.

inference statistics Exploratory or confirmatory statistical tests; see also DESCRIPTIVE STATISTICS.

informed consent EC (III): "the voluntary confirmation of a SUBJECT's willingness to participate in a particular trial and the documentation thereof; this information should only be sought after information has been given about the trial including an explanation of its objectives, potential benefits and risks and inconveniences, and of the subject's rights and responsibilities in accordance with the DECLARATION OF HELSINKI"; the possibility of third party review (MONITOR, health authority, insurance companies, CONTRACT HOUSES) of patient records should also be disclosed; doctor's failure to obtain i.c. may result at least in a finding of liability for negligence when injury occurs; i.c. is an absolute requirement except in an emergency situation or in a situation in which the patient is a child (in older children, that are able to read and write, both parents and the child may give their consent in writing) or incompetent, in which case consent is either implied or sought from a legal guardian; information and consent forms must be in a language that subjects understand and approved by an INSTITUTIONAL REVIEW BOARD (IRB); the consent form should be signed by the subject or its legally representative; a copy should be given to the person signing; oral consent is possible if testified by signature of the witness; forms however represent only one part of the entire consent process and do not preclude detailed oral explanations; GCP requires the following basic elements: statement that study involves research, identification of experimental procedures amongst other procedures, expected duration, risks or discomforts, benefits, extent of confidentiality of records, compensation and medical treatments if injury occurs, whom to contact for questions,

statement that participation is voluntary and that participation can be discontinued at any time without loss of benefits; the following additional elements apply when appropriate: unforeseeable risks (to foetus, embryo), participation terminated by investigator, additional costs to the subject, provision of significant new findings, approximate number of subjects involved, no preemption of other relevant laws, no limitation of other emergency medical care; FDA permits an IRB to waive the requirement to sign a written i.c. if: the research presents not more than MINIMAL RISK of harm to subjects, or involves only procedures for which written consent is not normally required outside the research context; see also EMERGENCY CONSENT WAIVER, LEGALLY ACCEPTABLE REPRESENTATIVE, PATIENT INFORMATION SHEET, RANDOMIZED CONSENT DESIGN.

informed consent application EMA: "(abriged) application for a product essentially similar to an authorised product where consent has been given by the existing marketing authorisation holder to use their data in support of this application; complete administrative and quality data should be provided with consent to preclinical and clinical data"; see also BIBLIOGRAPHICAL APPLICATION, DRUG MASTER FILE, GENERIC APPLICATION, MUTUAL RECOGNITION PROCEDURE.

ingredients see ADDITIVES.

initiation visit This visit finalises preparatory activities at a centre; the MONITOR or CLINICAL RESEARCH ASSOCIATE discusses with the INVESTIGATOR and his coworkers details of the study conduct, explains the use of the different forms (case record forms, drug accountability forms, informed consent forms a.s.o.), and leaves all necessary materials so that recruitment can be started right afterwards; see also PRESTUDY VISIT.

innovative chemical extension (ICE) Chemical variant of an already existing DRUG, usually with some extra therapeutic benefit; sometimes misleadingly called MEE-TOO.

innovative new drug (IND) see NEW CHEMICAL ENTITY.

inpatient Patient requiring hospitalisation for treatment (opp. OUTPATIENT).

in-process control EC (IV): "checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification; the control of the environment or equipment may also be regarded as a part of the i.-p. control".

inspection Basically, the purpose of an i. is the same as of an AUDIT: To ensure that activities are performed in accordance with commonly accepted standards

(GXP) and laws; audits are performed by independent internal or external groups, inspections by regulatory authorities; relevant authorities may conduct official inspections e.g., of clinical INVESTIGATORS, SPONSORS, INSTITUTIONAL REVIEW BOARDS and laboratories in order to verify adherence to regulations and GxP incl. GOOD CLINICAL PRACTICE and whether DATA submitted to authorities are substantiated by records; see AUDIT; types of i. are (FDA): "for cause" = as result of prior knowledge or suspicion (e.g. study outside the speciality of the investigator, results inconsistent with those of other studies, study has been publicized, sponsor alerts the agency, etc.) of alleged violations of regulations or when studies which are truly pivotal before the FDA are conducted outside the US; "expedited data audit" = directed at those studies under current review in the Division of Biopharmaceutics, but no decision has been made on the approvability of the applications the study support; "routine surveillance and assessment" = directed at those facilities not previously inspected; the result of the inspection is the ESTABLISHMENT INSPECTION REPORT; in the European area, pharmacovigilance-i. may be triggered mainly by circumstances concerning the MAH (first product placed on the market, never been inspected, merger, non-compliance with reporting requirements …), significant changes of the pharmacovigilance system or a specific product; fees and inspector's expenses are charged per inspector and day; see also AUDIT, CORRECTIVE AND PREVENTIVE ACTIONS, DATA QUALITY, FDA 483 FORM, FDA 484 FORM, MEMORANDUM OF UNDERSTANDING, QUALITY ASSURANCE PROFILE, SELF INSPECTION.

inspectional observations Observations during an inspection are usually classified into three categories: (i) "critical o." – i.e. Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data, or that poses a risk to public health or that represents a serious violation of applicable legislation and guidelines. (ii) "major o." – i.e. Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data or a deficiency in PV systems, practices or processes that could potentially adversely affects the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines; (iii) "other or minor o." – i.e. Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data; see also AUDIT, INSPECTION.

instant delivery see DELAYED RELEASE.

institution Any public or private entity or agency.

institutional review board (IRB) Sometimes also institutional review committee; American term for ETHICS COMMITTEE; any board or other group formally designated by an institution to review biomedical research involving humans as SUBJECT, to approve the initiation of and conduct periodic review of such research (INVESTIGATORS have also to report all changes in research activity and all unanticipated problems involving risks to subjects); to meet FDA requirements an IRB shall have at least five members, with varying backgrounds, possessing the necessary professional competence, including at least one member from a non-scientific area (lawyer, ethicist, clergy) and who is not otherwise affiliated with the institution; the IRB must consist of both sexes and no member may review a project in which it has conflicting interests; see also EXPEDITED REVIEW.

insurance EC (III): it is the responsibility of the SPONSOR to "provide adequate compensation/treatment for SUBJECTS in the event of trial related injury or death, and provide indemnity (legal and financial cover) for the INVESTIGATOR, except for claims resulting from malpractice and/or negligence"; clinical trial insurance is internationally not harmonized; at present usual limits for indemnity are in Germany € 500,000 for each research subject (examples for max. amount of coverage: Germany: € 1,000,000/event, UK: £ 5,000,000.00); liability can be on a "fault-based system" (an injured subject must prove that the investigator and/or drug manufacturer was at fault during the study) or based on a "NO-FAULT SYSTEM" or on a strict liability system (investigator or drug manufacturer must compensate an injured subject without regard whether either of party was at fault); see also CLINICAL TRIAL COMPENSATION GUIDELINES, COMPENSATION FOR DRUG INDUCED INJURY, INDEMNIFICATION, PRODUCT LIABILITY.

intangible costs Costs for pain and suffering; see ECONOMIC ANALYSIS.

integrated care WHO: "a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion".

integrated report Report of a clinical trial which integrates clinical and statistical descriptions, presentations, and analyses as well as information of the investigational plan and ethical procedures into a single report; the final study report should be submitted to the health authority(ies) within 1 year; see also REPORT.

integrative medicine Synthesis of conventional and unconventional (ALTERNATIVE, complementary) medicine in a holistic approach to the health of an individual; see also COMPLEMENTARY MEDICINE, FUNCTIONAL FOOD, ORTHOMOLECULAR MEDICINE, PHYTOMEDICINE.

intensive research design see SINGLE CASE STUDY; see also SAMPLE SIZE.

intensive monitoring System of record collation in designed areas such as hospitals or physicians in community practice (Vol. 9A); see also ADDITIONAL MONITORING, BLACK TRIANGLE, PHARMACOVIGILANCE, PRESCRIPTION-EVENT MONITORING, SOLICITED REPORTS.

intent-to-treat analysis (ITT-analysis) syn. intention-to-treat a., pragmatic a., management a., effectiveness a.; opp. actual-treated a./observed cases a., as-treated a; on (randomised) treatment a.; statistical analysis of DATA from all randomised patients, whether they were in full compliance with the study PROTOCOL or not, that is without omitting defaulters; the last values available from all patients are pooled for analysis (Last Visit Carried Forward – technique); ITT analysis ignores, in contrast to "as-treated" a., drop-outs (e.g. for ineffectiveness), missed doses, erroneous doses, wrong diagnosis a.s.o. and may lead therefore to inaccurate estimates of efficacy and toxicity; usually both types of analyses are provided for randomised CLINICAL TRIALS; a common approach for dealing with missing data is the "last observation carried forward" (LOCF) method; per-protocol a. are more likely to be subject to BIAS; other possibilities for analysis of results are A. OF ALL DOSED SUBJECTS or ALL ELIGIBLE PATIENTS; see also ANALYSIS OF STUDY RESULTS, EXPLANATORY TRIAL, INEVALUABILITY RATE, PER-PROTOCOL A.

intent-to-treat list syn. patient or SUBJECT SCREENING LOG; continuous list of patients which seem to be – at least theoretically and at first glance – suitable for inclusion in a trial (although, in fact, only part of the subjects will give their CONSENT or meet all INCLUSION and EXCLUSION CRITERIA); comments, why they were not eligible should be included in such a list; helpful for judgments concerning generalization of results (= external VALIDITY – degree to which the results valid in one patient population can be generalized to another) and for adjusting selection criteria in case recruitment is too slow; see also ENROLMENT LOG, SAMPLING ERROR.

interaction of drugs If two or more DRUGS are given at the same time the resulting effect(s) can either be the sum of the individual effects (additive e., no interaction), greater than the expected sum (multiplicative e., positive e., synergism) or less then expected (negative e., antagonism); DESIGNS suitable to detect interactions or to study two or more treatments simultaneously are e.g. FACTORIAL DESIGNS, CROSS-OVER DESIGNS, a.s.o.; the risk of drug interactions can be influenced by GENETIC POLYMORPHISM; see also BIOPHARMACEUTICAL, CYTOCHROMS P450, EFFECT MODIFIERS.

interaction study Clinical (pharmacokinetic, pharmacologic) study exploring the effects of one drug on the activity or properties of another drug.

interactive voice response system (IVRS) Computerised method of randomisation, tracking drug assignment to patients, drug use, and maintenance of drug inventory at clinical sites as well as at distribution centres; when a site needs to enrol a patient, the IVRS is contacted by public phone; the IVRS (which has a record of drug packages at the site) instructs the site to assign pack number NN and patient number MM to the patient; see also COMPUTERISED SYSTEMS, ELECTRONIC DATA CAPTURE, REMOTE DATA ENTRY, SOURCE DATA.

interfering variable see CONFOUNDER.

interim analysis Statistical analysis which is performed before the planned, total number of patients is recruited; for practical reasons i.a. should not be done before at least 50 (−75)% of the total number of planned cases are available; i.a. should always be planned in advance, since the likelihood of a false positive result (ALPHA ERROR) increases with the number of repeated tests (e.g. ten repeated tests on accumulating data at the 1 % level of significance during a trial will be about the same as an overall test for the trial at the 5 % level or three tests at the 5 % level will change the overall significance level to 11 %); i.a. demands therefore higher numbers of subjects; see also BONFERRONI CORRECTION, MULTIPLE COMPARISONS.

inter-individual comparison see BETWEEN-PATIENT COMPARISON.

intermediate product EC (IV): "partly processed material which must undergo further manufacturing steps before it becomes a BULK PRODUCT"; see also FINISHED PRODUCT, MEDICINAL PRODUCT.

internal audit see AUDIT.

international birth date (IBD) ICH: "The date of first MARKETING AUTHORISATION for a company's new medicinal product in any country in the world"; date on which the first regulatory authority granted marketing authorisation of a new drug; the "EU birth date" is the date it was first was authorised in the EU (these may be the same date); the "birth date" triggers the submission schedule for PERIODIC SAFETY UPDATE REPORTS; see also DEVELOPMENT INTERNATIONAL BIRTH DATE, EUROPEAN UNION REFERENCE DATE, HARMONISED BIRTH DATE, MARKETING EXCLUSIVITY.

International Classification of Diseases (ICD-9, ICD-10 – 9th, 10th edition of) the four digit WHO CODE for diseases; see also MEDDRA.

International Conference on Harmonisation (ICH) ICH was organised to provide an opportunity for tripartite harmonisation initiatives to be developed with input from both regulatory and industry representatives; ICH is concerned with harmonisation of technical requirements for the registration

of pharmaceutical products among three regions: The European Union, Japan and the United States; the six ICH sponsors are: The European Commission, the European Federation of Pharmaceutical Industries Association, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America; the ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA); the ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organisation, the Canadian Health Protection Branch, and the European Free Trade Area.

International Federation of Pharmaceutical Manufacturers Association (IFPMA) Federation founded 1968; it counts at present members from about 50 countries; one of the objects of the federation is to "promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on"; see also IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES.

International Federation of Pharmaceutical Physicians (IFAPP) The federation acts among other things as forum for cooperation between member associations and for dissemination of information on the specialty of pharmaceutical medicine as well as on the development and use of medicines; from its beginnings in 1972 to now over 30 national associations from countries all over the world have become members of IFAPP.

international non-proprietary name (INN) Name for a given DRUG (syn. GENERIC NAME, opp. Brand-/TRADE NAME); recommended by the WHO; initiated in 1950, the WHO-list contained 5,520 INNs in 1988 and 6,085 INNs in 1991; at present about 8,000 INNs have been published and this number is growing every year by some 120–150 new INN; INNs are, with some rare exceptions, identical to national names, e.g. local official names as British Approved Names (BAN), British Approved Name Modified (BANM), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN), United States Accepted Names (USAN), etc.; according to a naming convention, the following priority should be considered for the ranking of the name of a substance (chemical): INN, European Pharmacopoea (EU Ph.), BAN, International Union of Pure and Applied Chemistry (IUPAC), Summary of Product Characteristics (SPC); for herbal medicinal products/respective preparations the botanical Latin name should be used in accordance with the International Botanical Nomenclatural Code.

International Organization for Standardization (ISO) Worldwide federation of national standards bodies (ISO members), whereby members (governmental and non-governmental organizations) have the right to be represented on such committees; approval of ISO procedures requires at least 75 % approval by the members voting; standards are prepared by technical committees; appropriate standard to apply depends on activities of the company; see THEREFORE ISO 9000, ISO 9000–3, ISO 9001, ISO 9002, ISO 9003, ISO 10011–2.

international prescribing information see CORE DATA SHEET.

International Union of Pure and Applied Chemistry (IUPAC) see INTERNATIONAL NON-PROPRIETARY NAME.

inter-observer reliability Degree to which one observer classified observations in the same way as other observers; see also INTER-OBSERVER RELIABILITY, K STATISTIC.

interval estimation see CONFIDENCE INTERVAL, POINT ESTIMATION.

interval scale SCALE with measurements in definite units e.g. liters or ml, kg, etc.; see also DATA.

intervention trial syn. prevention trial, interventional t.; CLINICAL TRIAL studying prevention of DISEASE, either primary or secondary (e.g. reinfarction after infarction); see also LARGE SIMPLE TRIAL DESIGN, NON-INTERVENTIONAL TRIAL.

intra-individual comparison see K STATISTIC, WITHIN-PATIENT COMPARISON.

intra-observer reliability Degree to which one observer classified observations in the same way at different points in time; see also INTER-OBSERVER RELIABILITY, K STATISTIC.

intrinsic factors see EXTRINSIC FACTORS.

introductory meeting see OPENING MEETING.

invented name of a medicinal product, see TRADE NAME.

inventory see DRUG ACCOUNTABILITY.

investigational device exemption (IDE) Allows manufacturers to ship and use imported DEVICES intended solely for investigational use in human SUBJECTS, without having to first meet some FDA requirements; the IDE applies to all clinical studies that are undertaken to gather safety and EFFECTIVENESS DATA about a MEDICAL DEVICE; only sponsors of studies involving devices with a significant RISK (as determined by the local institutional review board) are required to submit an IDE application to the FDA (CDRH) for approval.

investigational drug syn. investigational product; any active ingredient, medicinal product or PLACEBO being tested or used in a clinical study; see also EXPERIMENTAL DRUG, FDA 356H FORM.

investigational drug brochure see INVESTIGATOR'S BROCHURE.

investigational drug labelling The package of an investigational new drug intended for human use has to bear a label with a statement specific for the national regulations; EC: name and address of the company, identification of the substance or code, date of expiry/retest, LOT number, name of the responsible physician, to be used for CLINICAL TRIALS; US: "caution: new drug – limited by federal law to investigational use".

investigational new drug (IND) syn. notice-of-claimed investigational exemption for a new drug; FDA: "An IND application is an application to start CLINICAL TRIALS with a new ACTIVE INGREDIENT"; see also CLINICAL TRIAL CERTIFICATE, CLINICAL TRIAL EXEMPTION, FDA 1571 FORM.

investigational medicinal product (IMP) EC: "a pharmaceutical form of an active substance or PLACEBO being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form"; a pharmaceutical product or vaccine used for a CLINICAL TRIAL; the term covers both, the (new) chemical entity or product of interest as well as the comparator but not a CHALLENGE AGENT, background therapy provided to all subjects or escape-/RESCUE MEDICATION; see also DRUG.

investigational medicinal product dossier (IMPD) The IMPD (full or simplified) gives information to justify the quality of any IMP to be used in the clinical trial, including reference products/comparators and placebos and includes summaries of information related to the quality, manufacture and control of the investigational medicinal product, data from non-clinical studies and from its clinical use; it is the basis for approval of clinical trials by the competent authorities in the EU; see also INVESTIGATOR'S BROCHURE.

investigational plan see PROTOCOL.

investigator syn. trialist; clinician(s) responsible for the practical performance of a clinical trial and for the integrity, health and welfare of the SUBJECTS during the trial; he must be legally allowed to practice, trained and experienced in research/performing CLINICAL TRIALS (in some countries a minimum experience with trials of 2 years is required, e.g. Germany), familiar with the background of the DRUG and the requirements of the study, reputated to have high

ethical standards and professional integrity; the legal status of persons authorised to act as investigators differs between states; coordinating i.: of a multicentre study, one single person who supervises or coordinates a trial and who is responsible for the medical and scientific conduct; primary (or principal) i.: one single person who supervises the medical conduct at an investigational site; the p.i. might not actually also conduct the investigation (see CO-INVESTIGATOR, SUB-INVESTIGATOR) or dispense the TEST ARTICLE in the event of an investigation conducted by a team of individuals; the p.i. is the responsible leader of that team, only one p.i. should be listed in item 1 Form FDA 1572; co-investigator means equal and shared responsibility for the conduct, control, and completion of a study; each coi. completes his own Form FDA 1572, item 1; sub-investigator means individuals assisting the investigator in conduct of the clinical investigation; examples: research fellows, residents, and associates; any physician who assists in a study should be listed as a subi. in item 6 on Form FDA 1572; responsibilities EC (III): "to be familiar with the product, to ensure that he has sufficient time, adequate staff and appropriate facilities, to provide retrospective DATA, to submit a curriculum vitae, notification/application to relevant bodies and to the ETHICS COMMITTEE, to obtain INFORMED CONSENT, to record of drug deliveries (DRUG ACCOUNTABILITY), to ensure dispensing of drugs only to trial subjects, to work according to the PROTOCOL and GOOD CLINICAL PRACTICE, to accept control procedures (MONITORING, AUDIT) to ensure confidentiality, to follow-up of subjects, to comment upon laboratory values outside a clinically accepted reference range …"; personal data of investigators are kept in the EU database; see also CONFIDENTIALITY, DATA PROTECTION ACT, PHYSICIAN INVESTIGATOR, STATEMENT OF INVESTIGATOR, STUDY COORDINATOR.

investigator's brochure (IB) syn. investigational drug brochure, clinical investigator's manual, investigator's drug brochure, investigator's manual; summary of all relevant information of an investigational product prior to the onset of a CLINICAL TRIAL by a clinician (preclinical DATA as chemical-, pharmaceutical-, toxicological-, pharmacokinetic-, pharmacodynamic data in animals and results of earlier clinical trials); the information must be updated in yearly intervals during the course of the trial and if new important data arise; the safety part overlaps with the safety information in the ANNUAL SAFETY UPDATE REPORT and the DEVELOPMENT SAFETY UPDATE REPORT; the IB can define those serious ADVERSE REACTIONS that do not request immediate reporting; there is considerable overlapping with the INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER; see also DEVELOPMENT SAFETY UPDATE REPORT, PRE-TRIAL DATA; for other types of documents see ANNUAL PROGRESS REPORT, ANNUAL SAFETY UPDATE REPORT (ASUR), REFERENCE SAFETY INFORMATION.

investigator's drug brochure see INVESTIGATOR'S BROCHURE.

investigator initiated trial (IIT) see NON-COMMERCIAL CLINICAL TRIAL, SPONSOR -INVESTIGATOR.

investigator's manual see INVESTIGATOR'S BROCHURE.

investigator's meeting see PRESTUDY MEETING.

investigator's site file (ISF) File of study documents kept at the investigational site, they strongly overlap with the trial master file, except a few essential documents such as the source documents, signed informed consent forms, "Subject Identification Code List" or the "Subject Enrolment Log" that are kept exclusively by the investigator.

investigator sponsored trial see NON-COMMERCIAL CLINICAL TRIAL; see also IN VITRO TOXICITY TESTING.

In vitro toxicity testing As part of the safety evaluation process of NEW CHEMICAL ENTITIES (NCE) a battery of tests exists for screening on general parameters such as cytotoxicity [e.g. Chinese Hamster Ovary cells (CHO), Ames test in bacterial cells], genotoxicity, phospholipidosis, steatosis and cholestasis; see also STEM CELLS, TOXICITY TEST.

ion trapping weak bases (e.g. alkaloids such as cocaine, amphetamine, narcotics) accumulate in the stomach even when given by parenteral route; at equilibrium across a membrane the concentration of the non-ionised moiety is the same on both sides (blood, gastric fluid) but more total drug is on the side on which the degree of ionisation is greater; see PARTITION COEFFICIENT, pKa.

ISO 9000/EN 29000 Specifies a worldwide quality management system (identical to the European EN 29000 and the British BS 5750); compliance with increases competition and decreases risk of professional liability; the ISO 9000 series consists of five parts of standards providing a generalised model for an organizational structure, responsibilities, procedures, and resources for implementing quality intentions concerning the production of pharmaceuticals, medical devices etc. or provision of services; EN 29000 is the identical European copy of the international standard ISO 9000; ISO 9000 standards must be followed in order to trade freely within the EC nations; companies that are not ISO 9000 accredited may need to undergo quality audits by every other company with which they trade; both ISO 9000 and FDA's good manufacturing practice regulations follow the same general guidelines; registration to ISO 9000 follows from satisfactory audit by certification bodies (e.g. BSI Quality Assurance, Lloyds Register Quality Assurance) with an initial total assessment (repeated every third year), followed by six monthly partial assessments; see also AUDIT, GOOD MANUFACTURING PRACTICE, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, QUALITY ASSURANCE, TOTAL QUALITY MANAGEMENT.

ISO 9000–3 Standard on quality management and QUALITY ASSURANCE for the development, supply, and maintenance of computer software, published by the International Organization for Standardization (ISO) in Geneva 1991; see also IEEE STANDARD 1062–1993, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION.

ISO 9001 Quality systems – model for quality assurance in design development, production, installation and servicing; for use when conformance to specified requirements is to be assured by the supplier during several stages which may include design/development, production, installation and servicing; first edition 1987; see also INTERNATIONAL ORGANIZATION FOR STANDARDIZATION.

ISO 9002 Quality systems – Model for quality assurance in production and installation; for use when conformance to specified requirements is to be assured by the supplier during production and installation; see also INTERNATIONAL ORGANIZATION FOR STANDARDIZATION.

ISO 9003 Quality systems – Model for quality assurance in final inspection and test; for use when conformance to specified requirements is to be assured by the supplier solely at final inspection and test; see also INTERNATIONAL ORGANIZATION FOR STANDARDIZATION.

ISO/DIS 10011–2 Guidelines for auditing quality systems – qualification criteria for auditors (1989); see also INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, AUDIT.

ISO country codes One to three letter CODE that may be used to replace the full name of the country heading. ISO 3166 codes together with the respective names of EU/EEA countries can be found at the following web site: http://publications.eu.int/code/en/en-370101.htm; ISO country codes are part of the "Worldwide unique case identification number" of ICSRs; see also INDIVIDUAL CASE SAFETY REPORT.

J

joint-marketing One product is sold by two companies under two TRADEMARKS; see also COMPETITION LAW, CO-PROMOTION.

joint-venture see: STRATEGIC ALLIANCE.

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K

Kaplan–Meier method syn. product-limit method; see SURVIVAL ANALYSIS.

Karch and Lasagna classification see CAUSALITY; see also STANDARDISED ASSESSMENT OF CAUSALITY.

Karnofsky performance status SCALE which was devised for use in trials of chemotherapeutic agents for carcinoma; 100 % = normal, no complaints, no evidence of DISEASE; 90 % = able to carry on normal activity, minor SIGNS or SYMPTOMS of disease; 80 % = normal activity with effort, some signs or symptoms of disease; 70 % = cares for self, unable to carry on normal activity or to do active work; 60 % = requires occasional assistance but is able to care for most of his needs; 50 % = requires considerable assistance and frequent medical care; 40 % = disabled, requires special care and assistance; 30 % = severely disabled, hospitalisation is indicated although death is not imminent; 20 % = very sick, hospitalisation necessary, active supportive treatment necessary; 10 % = moribund, fatal processes progressing rapidly; 0 % = dead; this scale however has never been validated; see also PERFORMANCE STATUS.

Keith–Wagener classification Describes the degree of retinopathy in hypertensive and arteriosclerotic patients (I–IV).

key efficacy criteria see PRIMARY ENDPOINTS.

key-punch error see CLERICAL ERROR.

kick-off symposium Marketing expression for a symposium arranged for launching of a new product.

kinetic Drugs are usually eliminated in one of three ways: zero order kinetics, first order kinetics, or a combination of both (Michaelis-Menten k.); zero order k. is a process whereby the rate of ELIMINATION is independent

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of the concentration of the drug, a fixed amount is eliminated over a period of time (capacity limited, dose dependent decrease), therefore small increments in dose may produce large increases in plasma concentration; frequently seen with drugs where liver enzymes are responsible for metabolism and which become saturated (examples: ethanol, acetylsalicylic acid, phenytoin); first order k.: the rate of drug elimination depends on the amount (concentration) of a drug present at a specific time; as the concentration falls, the process proceeds with a slower rate; the HALF-LIFE of elimination however remains constant; most drugs follow this process within their therapeutic ranges; Michaelis-Menten k.: refers to a mixed drug elimination pattern of both, zero- and first order k.

knowledge detection see DATA MINING.

Korotkoff sound first sound during auscultatory blood pressure measurement: first appearance of faint clear tapping sounds which gradually increase in intensity (the systolic pressure is heard for two consecutive beats and this correlates well with intra-arterial pressures; also the pressure at which pulse of arteria radialis/brachialis reappears); fourth sound: point of muffling of sounds, i.e. when the sounds stop to have a tapping character; fifth sound: complete disappearance of the sound (recorded as diastolic pressure).

Koseisho Japanese health ministry.

κ statistic Statistic used to measure interobserver or intraobserver agreement.

L

labelling FDA: "all labels and other written, printed or graphic matter upon any article or any of its containers or wrappers – or accompanying such article"; see also MISBRANDED DRUG; labelling of investigational drug samples for CLINICAL TRIALS requires, according to EC guidelines of good clinical practice (III), the following minimal amount of information: "For clinical trial", name of the responsible physician (INVESTIGATOR), identification-code of the trial, substance or patient code, dosage form, quantity, directions for use, storage conditions, expiry/retest date, producer, contact details (importer if manufacturer is outside the EU), "keep out of reach of children" (if taken home); for clinical trials of medicinal products for use before and during pregnancy: within the EC the following categories for labelling are used: A – product has been assessed, no harmful effects are known; B1 – safety not established, animal studies do not indicate harmful effects; B2 – safety not established, animal studies are insufficient to assess safety; B3 – safety not established, animal studies have shown reproductive toxicity; C – product does not increase spontaneous incidence of birth defects, but has potential hazardous pharmacological effects with respect to the course of pregnancy; D – product is known or suspect to cause birth defects and/or irreversible adverse effects on pregnancy outcome; it may also have potential hazardous pharmacological effects with respect to the course of pregnancy; see also ADVERSE DRUG EXPERIENCE, BLUE BOX REQUIREMENTS, INVESTIGATIONAL DRUG LABELLING, LABEL TEXT.

labelling phenomenon Means that the patient experiences an increased number of subjective symptoms (depression of mood, tiredness, anxiety etc.) after being informed of his/her diagnosis of e.g. hypertension or carcinoma; in general, the number of days of absence from work will also increase after being "labelled"; l.p. may be a considerable CONFOUNDER in clinical trials; see also HAWTHORNE EFFECT, PLACEBO EFFECT, WHITE-COAT HYPERTENSION.

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label text Requirements for label texts of a investigational medicinal products differ somewhat between countries; the following information has to be given routinely or may be requested in addition: name of drug or code, dosage, dosage form, route of administration, directions for use, quantity/volume, special storage conditions, special statements as: "keep out of reach of children", "for clinical trial only", caution statements etc., lot no., expiry or retest date, bottle no., study no., patient no., name of investigator, name of manufacturer, address of manufacturer; texts must be in the local language if the medication is handed out to the patient; for medicinal product (MP) that are placed on the market the following particulars must appear on the outer package (Dir 2001/83/EC): name of the MP (also in BRAILLE format) and generic name, form and strength, quantity of active substance per dose unit, excipients, route of administration, warning to keep out of reach of children, special warnings if necessary, expiry date, storage precautions, precautions for disposal of MP or waste material if appropriate, name + address of MAH, MA number, manufacturer's batch number, in case of self-medication instructions on the use; see also LABELLING.

label use American term for use of a drug for its approved indications.

laboratory normal range syn. reference range (preferred term), each laboratory has its own ranges within which values or results of a specific test can be considered as "normal", i.e. not pathologic; it is particularly important to have these ranges of each laboratory for the final interpretation of DATA; see also POOLING OF LAB DATA.

La Fontaine stages see FONTAINE'S STAGES.

large simple (trial) design Study design which is characterized by large sample sizes (data on population level rather than individual subject level), broad entry criteria consistent with the current, approved labelling, randomization based on equipoise (neither physician nor patient assumes one treatment being superior), minimal data collection requirements/key data normally available, hard, objective ENDPOINTS (death, stroke, hospitalization, etc.), follow-up minimizing interference with normal medical practice an whether or not a patient discontinued medication, minimal interventions consistent with current medical practice, INTENT-TO-TREAT ANALYSIS; LSTD is often used in vaccine research; see also DESIGN, ECOLOGICAL STUDY, EPIDEMIOLOGY, NON-INTERVENTIONAL STUDY, POST-APPROVAL RESEARCH, REGISTRY.

Lasagna's law The incidence of patient availability sharply decreases when a study begins and returns to its original level as soon as a study is completed (because most trialists overestimate the number of eligible patients); similar to MUENCH'S LAW, MURPHY'S LAW, PARETO'S PRINCIPLE.

last observation carried forward (LOCF) see LAST VALUE CARRIED FORWARD (LVCF).

last value carried forward (LVCF) syn. last observation/visit carried forward (eventually "baseline observation carried forward"); biometric technique whereby all DATA of all patients available are used for analysis; missing data are filled-up with the respective last value available and an "artificial" complete data base is created (single imputation); the opposite would be "complete case analysis" where incomplete cases/data sets are deleted. The alternative to both approaches would be is the MULTIPLE IMPUTATION APPROACH or MIXED MODEL OF REPEATED MEASURES (MMRM); LOCF tend to overestimate the treatment effect when there is a higher dropout-/withdrawal rate in the inferior group (e.g., placebo); see also ANALYSIS OF STUDY RESULTS, EXTENDER ANALYSIS, INTENT-TO-TREAT ANALYSIS.

last visit carried forward (LVCF) see LAST-VALUE-CARRIED-FORWARD.

latent period Time between exposure and development of clinical signs and symptoms; see also INCUBATION PERIOD.

Latin square CROSS-OVER DESIGN, where each of n patients (or of n groups of SUBJECTS) receives n treatments in a randomised order (represented by n× n squares); e.g. for three groups and three treatments: group 1: A, B, C; group 2: B, C, A; group 3: C, A, B; this design allows three different sources of variation to be equalised (three treatments, three groups of subjects, three orders); such a design can balance out any SEQUENCE (or site) effects as well as between-subject VARIANCES; frequently used e.g. in PHASE I, IIA or BIOEQUIVALENCE trials, but also for assessing observer variations; see also GRAECO-LATIN SQUARE.

Lead Ethics Committee see CENTRAL ETHICS COMMITTEE.

learning effect syn. practice e.; see SEQUENCE EFFECT; see also BIAS, CONFOUNDER, LABELLING PHENOMENON, PLACEBO EFFECT.

legally acceptable representative Individual, juridical or other person authorised under applicable law to consent on behalf of a subject (e.g., of a child, unconscious person) to it's participation in a clinical trial; see INFORMED CONSENT.

legal status Status of a medicinal product with respect to it's marketing authorization and conditions (e.g., dosage forms, indications, restrictions such as prescription by specialists only, limitation of the treatment duration/number of units, CONDITIONAL APPROVAL etc.); see also CONDITIONAL APPROVAL, MARKETING AUTHORISATION, RESTRICTED MARKETING AUTHORISATION.

lethality Number of subjects dying from a specific disease divided by the number of subjects suffering from this disease; see also CASE FATALITY RATE, MORBIDITY, MORTALITY.

LD-10 Dose (e.g. in mg/m^2) that is lethal in 10 % of the animals of the species treated; LD-50 tests of the past have now been replaced by increasing dose tolerance studies (see MAXIMUM NON-LETHAL DOSE).

liability see PRODUCT LIABILITY.

licence holder Pharmaceutical company that holds a marketing and/or manufacturing licence; see also MARKETING AUTHORISATION HOLDER.

licensed medicine see OFF-LABEL USE, UNLICENSED MEDICINE.

life-cycle management The classic life cycle phases of a pharmaceutical product are: introduction in major markets, expansion, maturity and decline as a result of competitive drugs and loss of patent protection; since risks concerning safety, costs of launching and establishing a new product are usually far greater than the costs of maintaining one already on the market there is a strong case for consciously extending the life of a product for as long as possible e.g., by new FORMULATIONS, new indications ("reprofiling" of a drug) or even "recycling" (after WITHDRAWAL from the market); increasing costs for R&D and budget pressure on public health systems tend also to favour well-established drugs for standard therapy; potency and side effects are often acceptable, whereas delivery and bioavailability may be less satisfactory; reformulation, including functional coating to improve pharmacological and or pharmacokinetic properties is often a strategy in l-c.m.; other major extension strategies are: acceptance s. The customer/doctor is encouraged to use the product (important: scientific and medical evidence); use expansion s. Broadening indications, providing evidence for safe use in other patient groups/higher dosages, LINE EXTENSION a.s.o.; profile enhancement s. Enhancement of the product-image; competitor response s. Prediction of and counteraction on competitor responses; cost-effectiveness s. Optimisation of effectiveness, minimisation of costs; see also COATING, CONTROLLED-RELEASE FORM, DRUG REPOSITIONING, EXCIPIENT, EXTENSION APPLICATION, FORMULATION, INNOVATIVE CHEMICAL ENTITY, NEW CHEMICAL ENTITY, RESEARCH AND DEVELOPMENT, TYPE II VARIATION.

life event Major life events (such as illness, marriage, pregnancy, death of relatives, children, new job, quarrels with superiors, move to a new home, vacations, loans taken, private bankruptcy etc.), can have effects on clinical outcomes and can bias results, esp. in QUALITY OF LIFE studies; see also BIAS.

life-table analysis see SURVIVAL ANALYSIS.

life-threatening FDA: "The patient was, in the view of the investigator, at immediate (emphasis added) risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had if occurred in a more serious form, might have caused death."

Likert scale Usually a 3 or 5 point SCALE for CATEGORICAL DATA (e.g. mild-moderate-sever); see also VISUAL ANALOGUE SCALE.

limits of impurity see IMPURITY.

Limulus Amebocyte lysate test (LAL) Test on the presence of bacterial endotoxins in drugs or devices in order to show effectiveness of depyrogenation techniques.

linear analogue self assessment (LASA) see VISUAL ANALOGUE SCALE.

linear correlation coefficient see CORRELATION COEFFICIENT.

linear no threshold (LNT) Hypothesis stating that a linear radiation dose – biological effect relationship exists with no lower limit, and leading to the conclusion that any dose, no matter how small, has harmful effects.

linear regression Process of fitting a straight line to two continuous variables; mathematically: $y = a + bx$; b = regression coefficient; predicts, in contrast to correlation coefficient r, value of y from a value of x; see also CORRELATION COEFFICIENT.

line extension New commercial form of a marketed product, e.g. new dosage or application form, new galenical formulation a.s.o.; strategy used for LIFE CYCLE MANAGEMENT of a pharmaceutical product; see EXTENSION APPLICATION.

liposome Vesicle constructed of phospholipid bilayers that allow the vesicles to mimic biological membranes; they contain aqueous phases between their bilayers; single-layered liposomes are generally <0.1–0.2 µm in size and good carriers of water-soluble DRUGS; their small size generally reduces their rate of elimination; multi-layered vesicles range from about 1–5 µm; with a higher proportion of lipid to aqueous phases due to multiple lipid bilayers, they are suitable for transporting lipophilic drugs; they are more rapidly cleared from the body than single-layered l.; see also DRUG DELIVERY SYSTEMS, FORMULATION.

listed adverse drug reaction ICH: "An ADVERSE REACTION whose nature and severity are consistent with the information included in the COMPANY CORE SAFETY INFORMATION"; see also UNLISTED ADVERSE DRUG REACTION.

literature controls see HISTORICAL CONTROL.

literature search Marketing Authorisation Holders are obliged to conduct in at least weekly intervals a l. search for adverse reactions reported with substances/products they have placed on the market, irrespective of their commercial status; it is essential to document the search strategy (search terms, languages, national/poorly indexed journals, key words, …) and databases used (e.g., Embase, Excerpta Medica, Medline, LILACS, etc.); search engines for

internet-based search of medical literature include Google, Google scholar, Yahoo search engine, etc., see also MASTER CASE, PERIODIC SAFETY UPDATE REPORT, PHARMACOVIGILANCE.

loading dose syn. priming dose; initial dose of a DRUG which is higher than the MAINTENANCE DOSE; the concept being to achieve a therapeutic concentration more rapidly in case of drugs with a slow elimination rate (e.g. therapy with tetracyclins, amiodarone, digitalis glycosides).

local CRA see CLINICAL RESEARCH ASSOCIATE.

local delivery see ROUTE OF ADMINISTRATION.

log sheet Record of documents such as e.g. case record form, test article accountability form.

loi DMOS abbr. "Diverses Mesures d'Ordre Social"; French law concerning financial benefits offered by the pharmaceutical industry to physicians and all other members of medical professions.

loi Huriet syn. Loi Huriet-Serusclat; French Medicines Act which came into operation in December 1988.

long-term use EC: "where the medicine is likely to be administered regularly over a substantial period of life, i.e. continuously during a minimum period of 6 months or frequently in an intermittent manner so that the total exposure is similar".

Lorentz-formula For calculating the ideal body-weight (w) of a subject; for men: w = (height [cm] − 100) − ((height − 150)/4); for women: w = (height − 100) − ((height − 150)/2); see also ANTHROPOMETRY, BODY-MASS-INDEX.

loss to follow-up Patients lost to a clinical trial without knowing the reasons; sometimes also used to describe the total number of patients lost, i.e. not finishing a particular clinical trial (premature termination); the FDA (Clinical Guidance Document, 1994) suggests that loss to follow-up should be less than 20 %; see also DROP-OUT, WITHDRAWAL.

lot FDA: "BATCH, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specific limits"; for stability information, a further characterisation as research-, pilot-, or production-lot, together with the lot number and the manufacturing date is generally requested.

lubricants see EXCIPIENTS.

M

macrobiotics unprocessed food such as whole grains; see FUNCTIONAL FOOD, ORTHOMOLECULAR MEDICINE.

magistral (magisterial) formula EC (I): "any MEDICINAL PRODUCT prepared in a pharmacy in accordance with a prescription for an individual patient"; see also OFFICINAL FORMULA.

maintenance dose Dose which should achieve an almost constant EFFECT without marked fluctuations in plasma concentrations; see LOADING DOSE.

Managed Care Organisation (MCO) Middleman in the insurance-based US health system; acts like a loss-adjuster on behalf of the insurance company or employer, to control and optimise the healthcare expenditure of the insured.

manufacture EC (IV): "all operations of purchase of materials and products, production, QUALITY CONTROL, release, storage, distribution of MEDICINAL PRODUCTS and the related controls".

manufacturer EC (IV): "holder of a manufacturing authorisation as described in article 16 of directive 75/319/EEC".

marginal costs Costs for one extra unit of product or service delivered; see ECONOMIC ANALYSIS.

marker see BIOMARKER, PROGNOSTIC/PREDICTIVE MARKER.

market see PHARMACEUTICAL MARKET.

marketing application syn. PRODUCT LICENSE APPLICATION; see NEW DRUG APPLICATION.

marketing authorisation (MA) Standard fees for obtaining m.a. (1 substance, 1 strength, 1 pharmaceutical form, 1996) are steadily increasing and

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were in USA: US$ 896,200 (2007); between 1990 and 2004 the FDA approved 1,284 new drugs including 431 new molecular entities (35 innovative new drugs in 2011); see also COMPLETE REVIEW LETTER, DRUG EVALUATION COST, LEGAL STATUS, MEDICINAL PRODUCT, NEW DRUG APPLICATION, PHARMACOVIGILANCE, PLACING ON THE MARKET, PRODUCT LICENCE APPLICATION, RENEWAL, SUNSET CLAUSE.

marketing authorisation holder (MAH) pharmaceutical company entitled to market a pharmaceutical product; in many cases this will be the same company as the marketing authorization applicant (MAA).

marketing authorisation under exceptional circumstances see CONDITIONAL APPROVAL.

marketing exclusivity Within the EC products registered by the CENTRALISED PROCEDURE will automatically benefit from a 10 year period of protection of innovation against use of the submitted DATA by second parties; an extension to 11 years is granted if one or more new indications have received authorisation ("significant clinical benefit" is demonstrated) during this period; in the event of there being no effective patent cover; a company's market share may decrease by 35 % in the first and by 50 % in the second year after the introduction of a competitive generic product; see also ESSENTIALLY SIMILAR MEDICINAL PRODUCT, HIGH-TECH MEDICINAL PRODUCTS, INTERNATIONAL BIRTH DATE, JOINT-MARKETING, ORPHAN DRUG, PARALLEL IMPORT.

marketing study Studies which are conducted in order to promote a product; such studies are de facto no longer allowed (Dir 2010/84/EC); they are also subject of REGULATIONS or CODES OF PRACTICE; esp. studies of PHASE IIIB and IV are frequently under the responsibility of marketing departments; see also IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES, MEDICAL OFFICE TRIAL, NON-INTERVENTIONAL STUDY, POST-AUTHORISATION SAFETY STUDY, POST-MARKETING STUDY.

masking see BLINDING.

master case Individual Case Safety Report (ICSR) concerning the same subject that has been transmitted by different reporters/sources and that exists in one or more duplicates (an issue particularly for literature-based cases); see also ADVERSE REACTION, CONSUMER REPORT, DUPLICATE REPORT, EUDRAVIGILANCE, INDIVIDUAL CASE SAFETY REPORT.

master file see DRUG MASTER FILE, TRIAL MASTER FILE.

master plan see STUDY LIST.

master record see DEVICE MASTER RECORD.

matched pairs see MINIMIZATION, RANDOMISATION.

maximum acceptable deviation (active ingredient content) see ACTIVE INGREDIENT, RADIOPHARMACEUTICAL.

maximum acceptable difference (MD) Largest true difference between treatments that a SUBJECT in the trial should be expected to accept and yet continue in the trial.

maximum admissible/allowed limit (MAL) see ALIMENTARY RISKS.

maximum non-lethal dose (MNLD) Highest single dose which does not induce death in animals; has replaced calculation of LD-50 values.

maximum recommended starting dose (MRSD) approach to calculate the starting dose of a new drug in first-in-human clinical trials; see PHASE I.

maximum repeatable dose (MRD) Dose which provides the first evidence of significant toxicity whereby the substance is administered in increasingly larger dosages – each 3–4 days – to the same group of animals; see also TOXICITY TESTS.

maximum residue limit (MRL) regulatory maximum limit of some chemicals in food; currently there are no such limits for acrylamide (in food such as bread or other baked products) or bisphenol A (in plastic containers) both of which are toxic.

maximum tolerated dose (MTD) Dose which provides the first evidence of treatment limiting toxicity; refers to: (1) moderate decrease in weight gain of animals, not exceeding 10 %, and usually determined on the base of results of 90 day studies; (2) anticancer drug evaluated in PHASE I patient trials in oncology; see DOSE ESCALATION STUDY, NOEL, TOXICITY TESTS.

maximum tolerated systemic exposure (MTSE) Dose escalation strategy in PHASE I clinical trials for drugs likely to have a clear concentration-effect relationship; see also CONTINUOUS REASSESSMENT METHOD (CRM), DOSE ESCALATION, FIBONACCI SEARCH SCHEME, PHARMACOKINETICALLY GUIDED DOSE ESCALATIONS (PGDE).

mean Arithmetic mean: average of a number of values (the sum of the values divided by the number of observations, $X = (x1 + x2 + \ldots xn)/n$); the geometric mean is defined as the n-root of the product of the values, $\lg X = (\lg x1 + \lg x2 + \ldots \lg xn)/n$; if the DATA are normally distributed the mean and MEDIAN coincide; see also MODE, DISTRIBUTION, POINT ESTIMATION, STANDARD ERROR.

mean blood pressure (MBP) see MEAN ARTERIAL BLOOD PRESSURE; see also KOROTKOFF SOUND, VITAL SIGNS.

mean arterial blood pressure (MAP) defined as: diastolic BP + 1/3 × (systolic − diastolic BP); see also PULSE PRESSURE, VITAL SIGNS.

measurement properties ACCURACY, CONSISTENCY, PRECISION, RELIABILITY, REPRODUCIBILITY, VALIDITY, VARIABILITY.

medDRA see CODE USED FOR ADVERSE EVENTS, MEDICAL DICTIONARY FOR DRUG REGULATORY ACTIVITIES; see also WHO-ADVERSE REACTION TERMINOLOGY.

median Midmost value of a distribution; 50 % of n observations have higher, and 50 % lower values, therefore = (n + 1)/2; see also DISTRIBUTION, MEAN, MODE.

medical audit Systematic, critical analysis of the quality of medical care, including the procedures used for diagnosis and treatment, the use of resources, the resulting outcome and the QUALITY OF LIFE for the patients; see also AUDIT, DRUG UTILISATION STUDY.

medical culture Differences in medical culture and traditions can induce clinical heterogeneity of DATA and are especially important when running MULTINATIONAL TRIALS or when comparing their results; examples for such differences and influence factors: prevalence of diseases, pharmaceutical expenditures, drug utilisation and self medication (OTC, herbal products), diagnostics, nutrition etc.; see also BIAS, CONFIDENCE INTERVAL, HEALTH CARE SERVICES, META-ANALYSIS, PRESCRIPTION, VARIABILITY.

medical device def. (EC): “any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the MANUFACTURER to be used for human beings solely or principally for the purposes of: diagnosis, prevention, MONITORING, treatment or alleviation of DISEASE, injury or HANDICAP, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means”; active m.d. means “any m.d. relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity”; active implantable m.d. means “any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure”; depending on the level of vulnerability, m.ds. are divided in four classes, class I, IIa, IIb and III (with increasing risk potential), for which different conformity and quality assessment procedures are requested; see CE MARKING, DEVICE, DRUG DELIVERY SYSTEMS, EC DECLARATION OF CONFORMITY, EC

TYPE-EXAMINATION, EC TYPE-EXAMINATION CERTIFICATE, INVESTIGATIONAL DEVICE EXEMPTION, MEDICAL DEVICE REPORTING, UNIQUE DEVICE IDENTIFICATION.

medical device reporting (MDR) Most regulations require that manufacturers, distributors or importers of devices REPORT to regulatory authorities when they become aware of information that one of their devices may have caused or contributed to a death or serious injury, or when a recurrent malfunction is likely to cause death or serious injury; EC: as "incidents" are considered "any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for the use" as well as "any technical or medical reason in relation to the characteristics or performance of a device … leading to systematic recall of devices of the same type"; reporting of death or serious injury has to be done to the FDA/health authority by phone as soon as possible, but not later than 5 calendar days, followed by a written report within 15 working days after initial receipt of information; see also DEVICE, INVESTIGATIONAL DEVICE EXEMPTION.

medical dictionary for drug regulatory activity (MedDRA) International standard for use in the entry, retrieval, analysis, presentation and communication of medical data in the regulatory context, for recording medical history and adverse events in clinical trials, registration dossiers, labelling and SUMMARIES OF PRODUCT CHARACTERISTICS, post-marketing safety surveillance/pharmacovigilance, the expedited reporting of adverse reactions and PERIODIC SAFETY UPDATE REPORTS; to be used in all phases of the lifecycle of a medicinal product; terms are grouped in a hierarchical classification system consisting of four primary levels of specificity; the "preferred term" (PT) is the most specific, the "system organ class" (SOC) the most general with 26 SOCs; "high level terms" (HLT) are contained within the system organ class; examples: tunnel vision (PT) – visual field disorders – eye disorders (SOC); rhabdomyolysis (PT) – muscular disorders (HLT) – musculoskeletal and connective tissue disorders (SOC); actually, the MedDRA (version 12.0) contains over 18,000 preferred terms; see also CODE, DATA MINING, WHO-ADVERSE REACTION TERMINOLOGY.

medical management see DISEASE MANAGEMENT.

medical office trial syn. GP trial, usually a MULTICENTRE TRIAL, done in general practice or other non-hospital units.

medical registry see REGISTRY.

medication error Patients can receive either the wrong drug, the wrong dose, the wrong route of administration or the right drug at the wrong time; in addition there can be simply omissions and extra doses as well as documentation

errors in the medical records; it is estimated that this occurs in at least 5–15 to 20 % of the cases; see also ERROR.

medication guide (US) see PATIENT INFORMATION LEAFLET.

medicinal gas EC: medicinal gases are classified as medicinal products; see also DRUG.

medicinal product EC (I): "any substance or combination of substances presented for treating or preventing DISEASE in human beings or animals"; syn. to the term drug (drug product) preferred by US regulations; in the EC, MARKETING AUTHORIZATION HOLDERS are obliged to submit basic information on their m.p. to a database maintained by the EMA according to Reg 726/2004 Art.57(2), e.g., on the marketing authorization status, country, RENEWAL date(s), EXCIPIENTS, indications and further key elements of the SUMMARY OF PRODUCT CHARACTERISTICS; see also BULK PRODUCT, DRUG, EUDRAVIGILANCE MEDICINAL PRODUCT DICTIONARY, FINISHED PRODUCT, INTERMEDIATE PRODUCT, PACKAGING MATERIAL, PROCEDURES, PRODUCTION.

Medicines and Healthcare Products Regulatory Agency Former Medicines Control Agency, MCA; part of the Department of Health; UK's licensing authority, responsible for safeguarding public health by ensuring that all medicines meet acceptable standards; responsible also for CLINICAL TRIAL EXEMPTION or CLINICAL TRIAL CERTIFICATE and INSPECTIONS; supported by other committees as the CSM, SEAR.

Medicines Control Agency (MCA) see MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA).

medwatch (US) The FDA safety information and adverse event reporting program of marketed medicinal products (http://www.fda.gov/medwatch/); in contrast to the "EUDRAVIGILANCE" system of the European Medicines Agency, medwatch accepts reports also directly from consumers (patients); see also ADVERSE EVENTS, PHARMACOVIGILANCE, YELLOW CARD SYSTEM.

mee-too syn. non-new molecular entities; see INNOVATIVE CHEMICAL EXTENSION.

mega-trial Controlled clinical trial enrolling very large numbers of subjects, usually over 10,000; see also CLINICAL TRIAL.

memorandum of understanding (MOU) FDA: allows mutual recognition of INSPECTIONS.

meta-analysis syn. pooled ANALYSIS, overview analysis; statistical analysis combining or integrating DATA from two or more independent trials of the same treatment, with similar selection criteria, and measuring identical parameters

by comparable methods; in general m.a. are performed for drawing global conclusions concerning safety and efficacy; when selecting studies from the literature, m.a. can be subject to severe publication BIAS; selection for inclusion in this kind of analysis should therefore proceed according to preset standards; a list of all included as well as excluded studies should always be presented and the sensitivity of the results of the m.a. against inclusion or exclusion of specific studies demonstrated; dangers: m.a. may invite false confidence in results where data differing in quality and patient groups differing in properties are combined; relationship between frequencies can be presented either as difference or as ratio (ODDS RATIO); see also BOX-SCORE REVIEW, FOREST PLOT, MEDICAL CULTURE, NARRATIVE REVIEW.

metabolism All biochemical activities carried out by an organism to maintain life; biochemical transformation of a drug; usually the body makes a drug more water soluble so the drug can be eliminated more rapidly via kidney and urine; common reactions of biotransformation include oxidation/hydroxylation, reduction and hydrolysis, or synthetic processes such as conjugation; for some enzymes genetic polymorphism has been described; e.g. for 4 out of approximately 8 isoenzymes of cytochrome P-450 (among African-Americans, 1.9 % lack debrisoquine hydroxylase CYP2D6 and 18.5 % mephenytoin hydroxylase CYPmp, essential for metabolisation of psychotropics) compared with 0–2.4 % (17.4–22 %) Asians and 3–8.9 % (2.5–6.7 %) Caucasians; important differences have also been reported for N-acetytransferase activity (NAT-2): 62 % of African-Americans lack the enzyme and are poor metabolisers compared to 5–21 % Asians and 49–74 % Caucasians; in these subjects for example isoniazid, a drug used in treating tuberculosis, causes a high incidence of peripheral neuropathy; see ADME, CYTOCHROME P450, ENANTIOMER, ETHNIC DIFFERENCES, GENETIC POLYMORPHISM, PHARMACOGENETICS, POOR METABOLISER.

metabolite A substance produced during or taking part in metabolism.

meta-data data about data; see also DERIVED VARIABLE.

Michaelis-Menten kinetics see KINETIC.

microbiology Study of living organisms and viruses, which can be seen only under a microscope; see also BACTERIUM.

microbiome Overall term for the number and variety of microbes that live in various habitats such as the intestines, oropharynx, skin, vagina etc.

microdose a dose that is less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance; see PHASE 0.

microdose study see PHASE 0.

micro-enterprise; Smallest category of "SMALL AND MEDIUM SIZED ENTERPRISES" (EC) with <10 employees and a turnover or balance sheet of ≤2 million Euro; such enterprises are exempt of a number of fees payable to EMA; see also EUROPEAN MEDICINES AGENCY.

micronucleus test Short term in vivo assay in rodent bone marrow in order to detect chromosomal damage to the mitotic apparatus by chemicals; see also ANEUGEN, CLASTOGEN, GENOTOXICITY, TOXICITY TESTS.

microparticles Short term for particles between 0.1 and 100 μm in size; see also DRUG DELIVERY SYSTEMS, FORMULATION, NANOPARTICLES.

microRNA (miRNA) Short, noncoding regulatory RNAs of about 22 nucleotides; miRNAs negatively regulate target gene expression at the post-transcriptional level through base pairing to complementary sequences in the 3' untranslated region (3'UTR) of targeted transcripts, inducing a combination of inhibition of translation and mRNA destabilisation; they are implicated in the regulation of biological processes such as cell growth, differentiation and APOPTOSIS; deregulation is involved in a number of diseases such as cancer, some types of viral infections, cardiovascular, inflammatory diseases and psychiatric disorders; see also NUCLEOTIDES, RNA INTERFERENCE.

microspheres see DRUG DELIVERY SYSTEMS, MICROPARTICLES.

middleware Software that connects different parts of an application and allows other software to interact.

migration study Study design in which disease occurrence in individuals who migrate to or from an area is compared with disease occurrence in individuals who do not migrate, in an attempt to separate genetic susceptibility from an environmental risk factor; since migrants are frequently different from those who stay in an area, and the number of individuals migrating who develop the disease is usually small, such studies are rarely informative; see also RISK.

minimal clinically important difference (MCID) see DELTA VALUE.

minimal bactericidal concentration (MBC) Minimal concentration (usually in mg/l) of an antibiotic which kills an organism; see also MINIMAL INHIBITORY CONCENTRATION.

minimal inhibitory concentration (MIC) Minimal concentration (usually in mg/l) of an antibiotic inhibiting growth of an organism; see also MINIMAL BACTERICIDAL CONCENTRATION.

minimal risk Risks or harm anticipated in the proposed research that are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

minimal toxic dose (MTD) Dose which just shows toxic effects; see NOEL, TOXICITY TESTS.

minimization Method in which patients are assigned to treatment groups so that the differences in known prognostic VARIABLES are minimized ("matched pairs"); e.g. in m. for the factors age (≤50 or >50), duration of disease (≤1 or >1 year) and pretreatment (yes or no) each patient appears once for each factor; then one adds together the number of patients in the corresponding three rows for treatment A as well as for B and assigns a new patient so that the difference between A and B is minimized; sometimes, e.g. in SINGLE CENTRE TRIALS, it may however be useful to introduce some element of chance by assigning the treatment with the smallest total sum with a probability <1 (e.g. ¾); used in comparisons to (historic) controls, rarely also as alternative to RANDOMIZATION.

minimum anticipated biological effect (MABEL); approach to calculate the starting dose of a new drug in first-in-human clinical trials; see PHASE I, see also DOSE ESCALATION STUDY.

minimum effective dosage (MED) Finding the MED by individual titration reduces costs and minimises ADVERSE EVENTS; dosage however should not be reduced to subtherapeutic levels as this has a detrimental effect on therapeutic EFFECTIVENESS and COST EFFECTIVENESS.

minimum inhibitory concentration (MIC) lowest concentration of an antibacterial agent that inhibits visible growth of a specific microorganism; see also ANTISEPTIC.

minimum relevant difference (MIREDIF) see DELTA VALUE.

minorities see WOMEN.

Minnesota code Code which can be up to three digits long and which is used for classifying electrocardiograms; published by the WHO.

misbranded drug DRUG or DEVICE with false or misleading LABELLING.

missing values Data may be missing at random or not (e.g., when drop-out rates between groups differ). In any case they are a challenge for statistical analyses especially in long-term clinical trials; as a rule of thumb, major problems can be expected if m.v. exceed about 30%; see also DROP-OUTS,

LAST VALUE (OBSERVATION) CARRIED FORWARD (LVCF, LOCF), MIXED MODELS REPEATED MEASURES (MMRM) MULTIPLE IMPUTATION APPROACH, WITHDRAWALS.

misuse syn. off-label use, unlicensed use; EC: "use of a medicinal product in a way which is not recommended (as authorized) in the SUMMARY OF PRODUCT CHARACTERISTICS"; cases of misuse without an adverse reaction are to be reported in the PSUR; see also DRUG ABUSE.

mixed model for repeated measures (MMRM) Likelihood-based model for accounting for missing values, usually focusing on repeated (continuous response) measures (observations at all time points) in contrast to the last value (observation) carried forward (LVCF, LOCF) approach that uses only the last (vs. first) value; see also MULTIPLE IMPUTATION APPROACH.

mode Most frequent single value of a range of data; distribution of data can be unimodal, bimodal a.s.o.; seldom used to describe frequency DISTRIBUTIONS, because it is not readily manipulated; see also MEAN, MEDIAN.

modified Fibonacci scheme see FIBONACCI SEARCH SCHEME.

modified release modification of the rate or place at which the active substance is released; principal types include CONTROLLED RELEASE, DELAYED RELEASE and PROLONGED RELEASE products (European Pharmacopoeia, EudraLex 3AQ19a: Quality of prolonged release oral solid dosage forms, Nov. 1992).

monitor Appropriately trained person appointed by the SPONSOR or a CONTRACT RESEARCH ORGANISATION (CRO) to be responsible to the sponsor or CRO for the performance, supervision and reporting on the progress of a CLINICAL TRIAL and for the verification of DATA; EC: "the m. must have qualifications and experience to enable a knowledgeable supervision of a particular trial"; trained technical assistants may help the m. in collection of DOCUMENTATION and subsequent processing; see also CLINICAL RESEARCH ASSOCIATE; responsibilities EC: "to control adherence to PROTOCOL, record of data and receipt of INFORMED CONSENT, to ensure information and communication, to check CASE REPORT FORM entries with SOURCE DOCUMENTS, to check the facilities of INVESTIGATOR, documentation of supply of product(s) (DRUG ACCOUNTABILITY), to assist the investigator in any necessary notification/application procedure and reporting, to submit written reports to the sponsor after each contact (monitoring report, AUDIT PAPER TRAIL, DATA TRAIL) …"; roughly estimated a monitor may have the capacity to run about 6–12 centres in parallel or 6 studies or 200 case report forms per year according to good clinical practice.

monitoring log list see MONITOR'S VISIT LOG LIST.

monitoring plan Document that describes the type of monitoring (e.g., on site vs. remote), frequency and extent of monitoring (e.g., 100% source document verification vs. random review of selected data, factors triggering an escalation); it may include details on the documentation of m. activities (such as m. reports, adaptive m., additional virtual m., deviation log) and m. responsibilities in addition.

monitoring report see INITIATION VISIT, MONITORING PLAN.

monitor's visit log list syn. appointment log book, site visit log, monitoring log list; list kept by the investigator in which each visit by the monitor or clinical research associate is entered and usually also signed off by a member of the investigational staff; not an "ESSENTIAL DOCUMENT".

monoclonal antibody Highly specific, purified antibody that is derived from only one clone of cells and recognizes only one antigen; such antibodies are also produced naturally during haematological malignancies (e.g., B-cell malignancies).

MOOSE Standards for reporting of Meta-analyses Of Observational Studies in Epidemiology, http://www.equator-network.og; see also PUBLICATION GUIDELINES.

morbidity Number of subjects suffering from a specific disease divided by total number of the population; usually given in number of cases/100,000; see also LETHALITY, MORTALITY.

mortality Number of subjects dying from a specific disease divided by the overall number of the population; usually given in number of cases/100,000; see also LETHALITY, MORBIDITY.

mortality rate syn. death rate; number of subjects in a specific group who die within a given number of person-years of follow-up.

Mosteller formula Formula to calculate the body surface area (BSA); BSA (m^2) = square root of {[weight (kg) × height (cm)]/3,600}; as the BSA is less affected by the body mass it is a better measure than body weight to adjust dosage of substances with a narrow THERAPEUTIC INDEX; see also ANTHROPOMETRY, BODY COMPOSITION, BODY SURFACE.

Muench's law see MÜNCH'S LAW.

multidrug resistance (MDR) ability of cells to develop resistance to a broad range of structurally and functionally unrelated drugs after exposure to a single drug; see also CHEMOSENSITIZER.

multicentre trial (MCT) syn. multi-investigator study; opp. single centre trial, SINGLE-SITE TRIAL; CLINICAL TRIAL conducted according to one single PROTOCOL in which the trial is identified as taking place at different investigational sites, therefore carried out by more than one INVESTIGATOR, but following the same practical details; usually one of the investigators is nominated as "COORDINATING INVESTIGATOR" who signs also the final report on behalf of all investigators; advantages versus single c.t.: better access to necessary SAMPLE SIZE, shorter duration, research ERRORS are less likely, better generalizability of results; a single centralised review of the scientific DESIGN is always recommended; risks of m.c.t. concern BIAS caused especially by site differences (in training, medical tradition, patient population, a.s.o.); m.c.t.s generally require a larger total number of subjects per treatment group to achieve the same POWER as that obtained in a single c.t. because of additional sources of variation; m.c.t.s are more complex concerning organization of meetings, elaboration of the protocol, standardization of methods for evaluation, e.g. rating scales, RANDOMIZATION, DATA collection, laboratory analyses, standardization (or transformation) of lab values with different reference ranges (or organization of a centralised analysis), drafting of the final REPORT, a.s.o.; care must also be given, that disproportions in the number of recruited subjects do not lead to statistical imbalances; see also GENIE SCORE, MEDICAL OFFICE TRIAL, MULTINATIONAL TRIAL.

multi-investigator study see MULTICENTRE TRIAL.

multinational trial MULTICENTRE TRIAL conducted in different countries at the same time, often because only moderate or difficult to quantify treatment effects are to be expected, demanding therefore larger patient numbers; problems (apart from that which are specific for multicentre trials) which might be encountered concern differences in MEDICAL CULTURE (classification, epidemiology, treatment of the DISEASE, different treatment facilities, diet, a.s.o.) as well as regulatory problems (export/import rules, regulation of supply of product(s), different legislation concerning preclinical requirements, INFORMED CONSENT, approvals, social welfare systems, a.s.o.).

multiple comparisons Statistical investigation comparing multiple groups with a control or with each other; see also BONFERRONI CORRECTION, INTERIM ANALYSIS, SUBGROUP ANALYSIS.

multiple imputation approach Missing or deficient values are replaced with two or more acceptable values that represent a distribution of possibilities (e.g., hypothetical result assuming the "best" resp. "worst" scenario); this statistical analysis requests to set up multiple data bases that contain some hypothetical data but have the advantage of being complete instead of the usual single, but incomplete database; see also EXTENDER ANALYSIS, INTENT-

TO-TREAT ANALYSIS, LAST VALUE CARRIED FORWARD, MIXED MODELS REPEATED MEASURES (MMRM).

multi-state procedure see DECENTRALISED PROCEDURE.

Münch's law First law: "In order to be realistic, the number of cases promised in any CLINICAL TRIAL must be divided by a factor of at least ten"; similar to LASAGNA'S LAW, sometimes also attributed to MURPHY (see MURPHY'S LAW; RECRUITMENT RATE); second law: "results can always be improved by omitting CONTROLS".

Murphy's law "if anything can go wrong it will"; often applied to describe problems concerning RECRUITMENT RATE (the number of available patients drops as soon as the trial starts, which is similar to MUENCH'S LAW and LASAGNA'S LAW); see also PARETO'S PRINCIPLE, PAROUZZI PRINCIPLE, PERUSSEL'S LAW.

mutagenicity tests MT reveal if a substance can change the genetic material of individuals or cells by gene mutations or chromosomal damage; the mutagenic potential of a substance can be tested by in vivo techniques (e.g. cytogenetic micronucleus test), or in vitro (e.g. AMES-TEST, HPRT, chromosomal aberration in human lymphocytes or Chinese hamster ovary (CHO) cells, V79 cells, unscheduled DNA synthesis (UDS) in human or animal cell lines); see also GENOTOXICITY, TOXICITY TESTS.

mutual recognition procedure (MRP) multistate procedure for a MEDICINAL PRODUCT that has already received a MA in at least one MS; to make it easier for obtaining marketing authorization in at least two further EC member states (concerned MS) by a common application after first having obtained marketing authorization in one member state (afterwards "RAPPORTEUR"); this country has a maximum of 210 days for approving the product; the initiating national authority creates an ASSESSMENT REPORT (for which it has additional 90 days), certifies the dossier and the SPC and submits it to other member states which have 90 days to recognise the decision; the maximum period is expected to be 390 days; the committee for proprietary medicinal products (CPMP) acts as arbiter if another member state will not recognise the first country's licensing decision; this multi-state procedure relates only to medicinal products authorised in accordance with the criteria laid down by the directives of the EC. It is possible to use the MRP more than once for subsequent applications to other Member States in relation to the same medicinal product (so called repeat use); see also DECENTRALISED PROCEDURE.

N

NAFTA see NORTH AMERICAN FREE TRADE AGREEMENT.

Nairobi principles Define rational drug use as "to ensure that the right drug is given to the right patient, at the right dose, and at affordable costs" (WHO-meeting in Nairobi, 1985); see also DISEASE MANAGEMENT, NAIROBI PRINCIPLES, PERSONALISED MEDICINE.

named patient use Prescription of a medication that has no (national) marketing authorisation for a single (named) patient in contrast to compassionate use that refers to a unspecified group of patients and not to an individual (Dir 2001/83/EC); usually the treating physician must care for the preparation and/or importation of the medication; see also EXPANDED-ACCESS PROGRAM, TREATMENT IND.

naming convention for substances (chemicals) see INTERNATIONAL NONPROPRIETARY NAME.

nanoparticles Nanoparticles are ultrafine particles sized between 1 and 100 nm thus similar to biological molecules such as proteins; they are able to pass through cell membranes and interact with proteins and other biopolymers; they are considered to be bio-persistent; their interactions with biological systems present possible dangers, both medically and environmentally which are relatively unknown; e.g., titanium dioxide (TiO2) or zinc oxide (ZnO) found in sunscreens has been shown to be toxic to DNA or colon cells resp. in small amounts, and food additives in processed meats have been linked to increased risk of diabetes type II and autoimmune diseases; TiO2 is also used by the pharmaceutical industry for coating/dying e.g. tablets; np are widely used e.g. in the cosmetic, food and textile industry; see also ALIMENTARY RISKS, DRUG DELIVERY SYSTEMS, FORMULATION, MICROPARTICLES.

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nanospheres see DRUG DELIVERY SYSTEMS, NANOPARTICLES.

Naranjo nomogram Scale to estimate the probability that an adverse reaction was caused by the drug in question; according to the total score of 10 questions the relationship is doubtful (<2), possible (2–4) or probable (5–8; Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245); see also DRUG INTERACTION PROBABILITY SCALE, STANDARDISED ASSESSMENT OF CAUSALITY.

Determining causality	Yes	No	Score
Are there previous conclusive reports of this reaction?	+1	0	
Did the ADR appear after the suspected drug was administered?	+2	−1	
Did the ADR improve when the drug was discontinued?	+1	0	
Did the ADR reappear when the drug was readministered?	+2	−1	
Are there alternative causes that could, on their own, have caused the ADR?	−1	+2	
Did the ADR reappear when a placebo was given?	−1	+1	
Was the drug detected in the blood or other fluids in known toxic concentrations?	+1	0	
Was the ADR more severe with increased doses/less severe with decreased doses?	+1	0	
Did the patient have a similar reaction to the same/similar drugs in previous exposures?	+1	0	
Was the ADR confirmed by any objective evidence?	+1	0	
Total score: doubtful (<2), possible (2–4), probable (5–8)			

narrative review A review without an explicit systematic approach concerning the synthesis of the results of the primary studies that are included; see also BOX-SCORE REVIEW, META-ANALYSIS.

national drug list Compendium of drugs available in a specific country; such lists contain not only the names but also the ATC codes (Anatomical Therapeutic Chemical Classification) and DDD values (Defined Daily Dose) of the respective medicinal product, e.g. Arzneimittelkompendium der Schweiz, Austria Codex (Austria), Dictionnaire Vidal (France), FASS (Sweden), L'Informatore Farmaceutico (Italy), Rote Liste (Germany); some countries such as Austria maintain public lists of specialities (https://pharmaweb.ages.at/index.jsf); see also COMMUNITY REGISTER, DRUG LIST, POSITIVE LIST.

national formulary see NATIONAL DRUG LIST, FORMULARY.

national register of medicinal products see NATIONAL DRUG LIST.

natural remedy syn. herbal remedies; see PHYTOMEDICINES, TRADITIONAL HERBAL MEDICINAL PRODUCT.

negative list syn. BLACK LIST (UK), opposite: POSITIVE LIST; list of medicines which are excluded from REIMBURSEMENT by national healthcare or insurance systems resp, existing in a number of countries such as France, Germany, Ireland, Italy, The Netherlands, Portugal, Spain and UK; see PRICE CONTROL.

neighbourhood control subjects Control subjects who are not hospitalised but live in the proximity to the hospital ("community controls"); such subjects may be found by door-to-door searches in close proximity to the residence of the case patient; see CONTROL, EPIDEMIOLOGY, EVALUATION TECHNIQUE, MATCHED PAIR.

neoadjuvant chemotherapy Systemic chemotherapy administered before the use of definitive locoregional treatment; this allows, if successful, tumour shrinking and reduces the risk of seeding of metastases by surgery; see also ADJUVANT CHEMOTHERAPY.

nested case–control studies Case–control studies that are "nested" within a COHORT study compare exposures in case patients (patients in the cohort who develop disease) and a sample of individuals in the cohort who have not developed disease; n.c.c. studies retain many of the advantages of cohort studies over case–control studies and are more cost-effective than cohort studies; see CASE-CONTROL STUDIES, CONTROL, DESIGN, EPIDEMIOLOGY, EVALUATION TECHNIQUE, MATCHED PAIR.

network chart see PROGRAM EVALUATION TECHNIQUE.

networking see STRATEGIC ALLIANCE.

new active substance (NAS) see NEW CHEMICAL ENTITY.

new chemical entity (NCE) syn. new active substance, new molecular entity; in 1990, it was estimated that the average NCE takes 12 years from synthesis to marketing approval, costs $231 million (DiMasi JA et al., J Health Econ 1991; 10:107–142), and needs 19 years of worldwide sales to recover RESEARCH AND DEVELOPMENT investment; according to estimates of 2004, development costs were around 1,150 million US$ and may increase to around 2 (4) billion US$ in 2009 (2012); 75 % of NCEs however fail to recoup their break-even point; in 1990, truly innovative NCEs accounted for roughly 10–30 % of all new registered drugs, the rest were "MEE-TOOS"; between 1975 and 1986 (12 years) more than 600 NCEs have been launched in Europe and the US; the proportion of

compounds synthesized to one NCE marketed is about 2,000:1–6,000:1; from over 50 NCE-approvals by the FDA in 1996 the number has steadily decreased to 24 in 2002 and fluctuates around 20 per year; see also INNOVATIVE CHEMICAL EXTENSION, LIFE CYCLE MANAGEMENT, RESEARCH AND DEVELOPMENT, TOXICITY TESTING.

new drug application (NDA) Application for marketing approval (US); FDA requests at least two independent, well-controlled clinical trials providing "substantial evidence" to gain approval, but approval has also been granted on the basis of one well-controlled clinical trial and confirmatory evidence form preclinical and clinical trials; the typical NDA approved in the mid-1990s came in with data from more than 80 clinical trials, but only 3–14 of them providing substantial evidence, and with 9–65 % being "failed" studies; review for NDA by the FDA takes about 20 months and costs which are charged by the FDA may be in the order of ~900,000.00 $ (~500,000 in 1994); between 2005 and 2009 pharmaceutical companies in the US spent >3 billion US$ on R & D but only 34 new products received marketing authorization by the FDA; see also ESTABLISHMENT LICENCE APPLICATION, FDA 356h FORM, PRODUCT LICENCE APPLICATION, more and more electronic submission schemes are also coming in use such as SMART (Submission Management and Review Tracking) of the FDA and the CANDA (Computer Assisted New Drug Application); the basic fee for a NDA is € 242,600 (EMA 2008, single strength, one pharmaceutical form, one presentation); see also MARKETING AUTHORISATION.

new drug development plan (NDDP) Defines key elements and activities (requirements) for new drug development as well as specifications that are in effect during the product development (US); see also DRUG.

new molecular entity (NME) see NEW CHEMICAL ENTITY.

New York Heart Association classification (NYHA) Classification of heart failure; I = no limitation of physical activity; II = slight limitation of physical activity; III = marked limitation of physical activity; IV = inability to carry out any physical activity without discomfort.

Neyman fallacy ERROR committed by using prevalent cases rather than newly diagnosed cases; this may lead to evaluation of exposures that are associated with survival rather than cause of disease; see also BIAS.

NLN see NORDIC COUNCIL OF MEDICINES.

NOAEL abbr. no-observe adverse event level in repeated dose toxicity studies with animals, i.e. highest tested dose without toxic effects; see NOEL, PHASE I, see also DOSE ESCALATION STUDY.

N of 1 study see SINGLE CASE EXPERIMENT.

no carbon required paper (NCR) Paper that automatically makes copies; often used for CASE RECORD FORMS and ADVERSE EXPERIENCE reports.

no-effect level see NOEL.

NOEL syn. NOAEL; abbr. no-effect level in chronic TOXICITY studies with animals, i.e. highest tested dose without toxic effects.

no-fault insurance syn.: no-fault compensation (opposite: fault system); guarantees compensation for persons injured, distressed or subjected to unnecessary pain or suffering as a result of activities comprising the CLINICAL TRIAL independently of the legal liability of the person or body making payment and without regard to a causal relationship to the INVESTIGATIONAL DRUG; the patient or non-patient volunteer would thus not have to seek recompense through proving negligence but would only have to show that the trial PROTOCOL was being adhered to; compensation for death or injury which arise from a departure from the protocol or is attributable to the fault of negligence of a third party or of a patient will be excluded from such policies; see also INDEMNITY, INSURANCE, LIABILITY.

nominal data syn. categorical d., dichotomous d.; DATA fitting into one of two (or more) categories, whereby categories of the responses are assumed not to be overlapping for the analysis, e.g. alive or dead or responses to multiple choice questions; suitable statistical tests for unpaired samples can be Fischer's exact test or chi-square test with Yate's correction, for paired samples Sign or McNemar's test; other non-parametric methods of analysis which may be suitable are e.g. Wilcoxon test, Friedmans or chi-squared goodness of fit tests; see DATA.

non-alpha site syn. non-academic site; clinical trial site which is e.g. a GP or a specialist outside of a teaching or university hospital; involving of such sites in clinical trials increases a study findings' applicability to the entire population because of differences in the patient population; see POSTMARKETING SURVEILLANCE.

non-commercial clinical trial (EC) syn. "Sponsor-Investigator study" (ICH), investigator-initiated trial (IIT), Investigator Driven Clinical Trial (IDCT), investigator sponsored trial, "academic study" (in contrast to a "commercial" study sponsored by the pharmaceutical industry); EC: Clinical trials conducted by researchers without the participation of the pharmaceutical industry; non-c. CTs are designed, conducted and reported under the control of the investigator(s), data and results are also owned by them; such trials cannot be used for marketing authorization; non-c CTs seem to be less likely to report positive outcomes

(61 % vs 85 %, www.annals.og/content/153/3/158.abstract); actually less then 20 % of the clinical trials notified to EUDRACT are non-c. CTs with a decreasing trend; see NON-INTERVENTIONAL STUDY, PHYSICIAN-INVESTIGATOR, SPONSOR-INVESTIGATOR.

non-comparative study Unblinded (open) study without CONTROL group; although lack of controls will most often lead to the problem of confounding by the indication, comparative studies are not always necessary//ethically justified to evaluate drug efficacy esp. in the following examples: (1) drug effect is very dramatic (e.g. prompt awakening of a patient who is comatose from an overdose of methadone when naloxone is administered), (2) predictable, invariable, progressive disease without therapy (e.g. scurvy, if vitamin C is not administered), (3) disease with no spontaneous cure (e.g. gonorrhoea, treatment with suitable antibiotic); see also CLINICAL TRIAL, EFFECT SIZE, Q-VALUE.

non-compliance Failure to take prescription drugs properly; see COMPLIANCE.

non-conventional medicine syn. alternative or complementary or traditional medicine; see ALTERNATIVE MEDICINE.

non-evaluable patient At the end of clinical trials there are almost regularly good arguments to exclude data of some patients for parts of the efficacy analyses, e.g. for the following reasons: early DROP-OUT, non-responder with progression of disease, violation of INCLUSION or EXCLUSION CRITERIA, lack of COMPLIANCE, intercurrent illness, comedication which was not allowed by the protocol, a.s.o.; see also INTENT-TO-TREAT ANALYSIS, PROTOCOL DEVIATION.

non-experimental trial see NON-INTERVENTIONAL TRIAL.

non-interventional trial syn. non-interventional study (NIS), non-experimental trial (study), OBSERVATIONAL STUDY (EC); EU: "a clinical trial where the selection of subjects or the attribution of medicinal products or the examinations carried out or medical and biological follow-up of subjects falls within current medical practice"; relevant findings have to be summarized in the respective PERIODIC SAFETY UPDATE REPORT; see also INTERVENTION TRIAL, LARGE SIMPLE TRIAL DESIGN, LOW-INTERVENTION CLINICAL TRIAL, POST-AUTHORISATION STUDY, POST MARKETING SURVEILLANCE.

non-investigational medicinal product (NIMP) A medicinal product with a MARKETING AUTHORISATION (MA) valid throughout the European Community or in one or more Member States; in clinical studies, NIMPs should be supplied in the commercial available package and must be used according to the MA (otherwise it is a IMP); product liability applies; see AUXILIARY MEDICINAL PRODUCT (AMP), INVESTIGATIONAL MEDICINAL PRODUCT.

non-new molecular entities (non-NME), see MEE-TOO.

non-prescription drug see OVER-THE-COUNTER.

non-renewal see WITHDRAWAL.

non-serious adverse reactions of marketed medicinal products are to be reported to the authority within 90 days at the latest (Dir 2010/84/EC; before, the had to be reported only in the PSUR); see ADVERSE REACTION.

non-therapeutic study Study without any therapeutic benefit for the subject; see also PHASE I.

Nordic Council on Medicines (NLN) Forum of cooperation on drug affaires between Denmark, Finland, Iceland, Norway, and Sweden which was set up in 1975 and produced the Nordic Guidelines on good clinical practice; see also GOOD CLINICAL TRIAL PRACTICE.

Nordic Guidelines Guidelines on good clinical practice produced by the NLN and published first in 1989 1 year before the EC guidelines, followed by GCP Guidelines of the WHO; see GOOD CLINICAL TRIAL PRACTICE.

normal distribution see DISTRIBUTION.

normal range see LABORATORY NORMAL RANGE.

North American Free Trade Agreement (NAFTA) Agreement between the US, Canada and Mexico for a free trade area with approx. 360 million people and an annual economy of around 6,000,000 million US $.

note for guidance syn. guide, guideline; see EC LAW.

notice-of-change form see DATA RESOLUTION FORM.

notice-of-claimed investigational exemption for a new drug see INVESTIGATIONAL NEW DRUG.

no-treatment-control DESIGN comparing active treatment vs. no-treatment; can be subject to severe BIAS due to the PLACEBO- or HAWTHORNE EFFECT.

nucleotides Molecules that are units building up much molecules like ribonucleic acid (RNA) and desoxyribonucleic acid (DNA); they are commonly abbreviated (IUPAC nomenclature) by symbols such as A (adenine), C (cytosine), G (guanine), T (thymine), U (uracil).

nuisance variable see CONFOUNDER.

null-hypothesis (Ho) Statistical term for assuming no difference between treatments; when rejecting Ho there is still a risk of committing an ALPHA ERROR, when accepting Ho a BETA ERROR can occur.

nullification Message informing the receiver organization that a case (ICSR) should be nullified (inactivated) in the database; for AUDIT TRAIL reasons it cannot be completely eliminated.

Number Needed to Harm (NNH) Number of patients that need to be treated in order to observe one withdrawal due to adverse reactions; sometimes used to compare the tolerance of treatments; see also NUMBER NEEDED TO TREAT.

Number Needed to Treat (NNT) Number of patients that need to be treated in order to observe one case with the desired treatment effect (e.g., complete cure, reduction of pain intensity by 50 %); see SAMPLE SIZE ESTIMATION.

number of observations (n) The sample size n of normally distributed data can be small, about 2–3 (e.g. measurements of blood pressure for one subject at one time), in case of symmetric but not bell-shaped data about 10–15, for skewed data 50–100.

number of patients see SAMPLE SIZE ESTIMATION.

numerical pain scale (NPS) see VISUAL ANALOGUE SCALE.

Nuremberg Code (German: Nürnberg) Code on ethical considerations for conducting research on human beings; most regulatory codes and medical research policies throughout the world are based on these 10 conditions set forth in the N.C. in 1947 (voluntary consent of subjects, fruitful results for the good of society, experiment justified on results in animals, avoiding injury, risk never exceeding humanitarian importance, protection of the subject, scientifically qualified investigators, liberty to withdraw consent, termination of the experiment if subjects are likely to be harmed); see also DECLARATION OF HELSINKI.

Nutley system glossary see CODE.

nutraceutical Nutritional product with relevant health effects; syn. used with FUNCTIONAL FOOD; see also FOOD SUPPLEMENT, NUTRITIONAL/DIETARY SUPPLEMENT.

nutrients are vitamins and minerals such as from the normal diet; they may be used as FOOD SUPPLEMENTS; see also DRUG, FUNCTIONAL FOOD, NUTRACEUTICAL, PHYTOMEDICINES, RECOMMENDED DIETARY ALLOWANCE, TRADITIONAL HERBAL MEDICINAL PRODUCT.

nutrigenomics Functional food individually adapted to genetic predisposition(s); in the EC, health-related information is authorized in form of comments that the respective FUNCTIONAL FOOD can improve or increase specific body function(s) or decrease risks (e.g., improved mineralization of bones by increased calcium supply); see also FOOD SUPPLEMENTS.

nutritional status see BODY COMPOSITION.

nutritional supplement syn. dietary supplement; see FOOD SUPPLEMENT, NUTRACEUTICAL.

O

obesity see ANTHROPOMETRIC MEASUREMENTS, BODY COMPOSITION, BODY-MASS-INDEX (QUETELET'S INDEX), LORENTZ FORMULA, ROHRER INDEX, WAIST CIRCUMFERENCE, WEIGHT.

objective endpoint see PRIMARY ENDPOINT.

O'Brian procedure (modified) Statistical test procedure, based on the t-test, that allows to use multiple endpoints; see also PRIMARY ENDPOINT, WEI-LACHIN PROCEDURE.

observation syn. finding; an observation (during an audit, inspection) is defined as deviation from Sponsor's/CRO's SOPs, protocol, accepted standards, appropriate guidelines (ICH), and/or regulatory requirement incl. applicable laws; o. are usually graded in three categories: "critical" – a deviation that poses a potential RISK to public health or that represents a serious violation of applicable legislation and guidelines or that is suspicious to fraud; "major" – a deficiency that represents a violation of applicable legislation and guidelines or a deviation from accepted standards that could potentially pose a risk to public health; "minor" – a deviation that is neither critical nor major; see also INSPECTIONAL OBSERVATION.

observational study (ICH), Non-experimental, open label, uncontrolled study, usually done in phase iv (post-marketing observational study); they may be useful to study how doctors actually practice, and how drugs actually perform because patient selection in controlled clinical trials often limits generalisation of results; such o.s. are indicated when practical or ethical considerations render randomized clinical trials infeasible, e.g. in surgery; objections made frequently are that results provided by such a design can easily be manipulated; o. studies can be comparative (e.g., CROSS-SECTIONAL STUDIES, CASE–CONTROL STUDIES, and COHORT STUDIES, both retrospective

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and prospective); see also CASE SERIES, DESIGN, NON-COMPARATIVE STUDY, NON-INTERVENTIONAL STUDY (NIS), PHARMACOVIGILANCE, REGISTRY.

observed cases analysis see INTENT-TO-TREAT ANALYSIS.

odds The o. of a specific event is the ratio of the probability of its occurrence divided by its probability of non-occurrence; see META-ANALYSIS.

odds ratio (OR) Ratio of two ODDS i.e. of probabilities of occurrences; o.r. is a good estimate of the true relative risk of exposure in the target population, provided outcome is rare; OR is commonly used in cross-sectional or cohort studies; see META-ANALYSIS.

officinal formula EC (I): "any MEDICINAL PRODUCT which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question"; see also MAGISTRAL FORMULA.

off-label use syn. off-license or unlicensed or misuse; term for use of a drug in other than approved indications (opp. LABEL USE); most national laws allow physicians the o.l.u. as "ultima ratio", if no other approved treatments will be effective; the marketing authorization holder is responsible for "reporting any use of the medicinal product which is outside the terms of the marketing authorization" (Dir 2010/84/EC); a use "contra-label" however is a medical error with possibly legal consequences; see also MISUSE, UNLICENSED USE.

off-license see OFF-LABEL USE.

ointment see FORMULATION.

old see ELDERLY, GERIATRIC EVALUATIONS.

oldest old individuals >85 years; see AGE GROUPS, ELDERLY, GERIATRIC EVALUATIONS.

old substance For substances with a long-term marketing experience, e.g. penicillin or acetylsalicylic acid, the CPMP has recommended that requirements for toxicological and clinical testing can be limited to areas of new scientific developments.

oncogene Any of a family of cellular DNA sequences which possess the potential to become malignant by undergoing alteration. There are 4 groups of viral and non-viral oncogenes: protein kinases, GTPases, nuclear proteins, and growth factors.

oncogenicity studies syn. carcinogenicity tests; lifetime studies conducted in animals to detect whether a compound can cause neoplastic changes in tissues

or not; such tests are usually required as part of the clinical development of a drug when: (1) the substance will be used continuously for long periods (USA: over 6 weeks) or have a frequent intermittent use, (2) the chemical structure suggests carcinogenic potential, (3) special findings with other compounds of this class or with metabolites indicate such a potential; see also GENOTOXICITY, TOXICITY TESTS.

oncology Science on tumours.

one sample multiple testing design D. controlling rejection of a drug or hypothesis from further study similar to GEHAN'S DESIGN; example: 15 patients are treated – if no response occurred, the probability of a success is <20 %, accepting an error rate of 5 %; if at least 4 responses occurred, the hypothesis of a success rate >20 % is accepted; in a second stage the number of treated individuals can be raised to 25, where the drug can be rejected when 3 or fewer responses have been observed.

one-sided test see ONE-TAILED TEST.

one-tailed test syn. one-sided test; opp. TWO-TAILED TEST; sometimes used in studies in which the difference in outcome is said to be of interest in one direction only, e.g. when the experimental treatment entails greater risks or costs than the standard treatment and would therefore be recommended only in case of a proven advantage; one-tailed tests are often appropriate when comparisons of surgical vs. medical treatments are made, because in general the medical treatment would be preferred.

onset-adjusted incidence rate Number of new disease onsets (defined by date of onset of symptoms, not diagnosis) in a fixed population; see INCIDENCE RATE, ONSET-ADJUSTED PREVALENCE.

onset adjusted prevalence Number of individuals with disease (defined by date of onset of symptoms, not diagnosis) in a population on a specific date; see INCIDENCE RATE, ONSET-ADJUSTED INCIDENCE RATE, PREVALENCE RATE.

on-site audit see AUDIT.

opening meeting syn. introductory meeting; meeting of an auditor or inspector with the auditees before starting an audit/inspection where purposes of the audit and organizational aspects concerning the activities are discussed; see also EXIT INTERVIEW/CLOSING/CLOSE OUT MEETING.

open study Any study where subjects and investigators are not blind to treatment assignment; see BIAS, DESIGN, NON-COMPARATIVE STUDY, OBSERVATIONAL STUDY, UNBLINDED STUDY, UNCONTROLLED STUDY.

open system Opposite to closed system; FDA: "computerized system whereby access is not controlled by persons responsible for the content of ELECTRONIC RECORDS that are on the system"; see also CLOSED SYSTEMS, COMPUTERISED SYSTEM, ELECTRONIC SIGNATURE.

optical activity see CHIRALITY.

optical character recognition see ELECTRONIC DATA CAPTURE.

optical mark recognition see BARE CODE.

order effect see SEQUENCE EFFECT.

ordinal data Data which have finite boundaries, e.g. quasi-quantitative data or data which include subjective measurements such as VISUAL ANALOGUE SCALES or which can be ranked into three or more categories, e.g. mild, moderate, severe; suitable statistical tests are e.g. for two groups, unpaired samples the Mann–Whitney U or median test, for two groups, paired samples Wilcoxon signed-ranks test, for multiple groups, unpaired samples Kruskal–Wallis one way analysis of variance and for multiple groups, paired samples Friedman two-way analysis of variance; see DATA.

ordinal scale SCALES frequently used in CLINICAL TRIALS to quantify phenomena or outcomes which are non-dimensional, either as a "single state" s. (scale is designed to measure patients at a single point in time), e.g. patients state at entry and at the trial's conclusion, such as the WHO-PERFORMANCE STATUS, the KEITH–WAGENER classification for hypertensive retinopathy, the Kurtzke score in multiple sclerosis or the RITCHIE INDEX in rheumatology, or as "transition" s. (measuring magnitude and direction of changes directly and symmetrically, without baseline – time 1 assessment – e.g. −2 much worse, −1 worse, 0 the same, +1 better, +2 much better); when using o.s. a few rules should be followed: (1) individual elements of the s. should be clearly defined, and must assess the same phenomena; (2) ranks should be discrete, non-overlapping (mutually exclusive) and in a reasonable, hierarchical order; (3) scale scores should be placed in a clinical context and should detect both improvement and deterioration without clustering subjects at one extreme on the s.; (4) correct analyses should be concentrated on within-patient changes, concordance (similar, correlating trends) with other outcome measures should be shown; finally, increments from one rank to the next are usually far from linear and (++) does not mean twice as good or worse than (+); although scales can be made more sensitive by increasing the number of levels of severity this is usually accompanied by reduced RELIABILITY; see also QUALITY OF LIFE SCALE, SCALE, SCORE, VALIDITY, VISUAL ANALOG SCALE.

original medical record see SOURCE DATA.

orphan diseases The estimated number of "rare" (orphan) DISEASES (ROD) is about 5,000–7,000; WHO: pathological conditions affecting 65–100/100,000 of the general population; FDA: incidence <20/100,000; EC: ≤50/100,000 (Reg. 141/2000/EC); Japan; 50,000 Japanese patients, Australia: 2,000 Australian patients; about 6,000–8,000 of the estimated 30,000 disease entities known are o.d., about 80 % o.d. have a genetic origin and most of them affect patients already during childhood; only about 5 % have a licensed medication; see also http://www.orpha.net/censor/cgi-bin/index.php, AUTOIMMUNE DISEASE, FAST-TRACK PROCEDURE, GENETIC DISEASES, GENETIC VARIANCE, LICENSED MEDICINE, ORPHAN DRUG.

orphan drug DRUG or medical equipment for a narrow indication (rare disease, ORPHAN DISEASE); in US a drug may be designated and registered as o.d., receiving a 7 years marketing exclusivity if the number of patients will not exceed an estimated maximum of 200,000 cases in a year, i.e. a prevalence <1/1,250; EC: 10 years marketing exclusivity if the prevalence does not exceed 5/10,000 of the EU population, (i.e.. 188,800 persons of an estimated population of 377.6 million in the Community as per 1 January 2001); similar incentives have been introduced in Japan (limit: Japan: 50,000 cases/year), Singapore and Australia; in Japan regulations will facilitate also development of o.d.s and medical devices if the target population is estimated to be less than 50,000 cases and development medically necessary (special tax incentives, preferential regulatory review, re-examination period for POST-MARKETING SURVEILLANCE and ADVERSE REACTION data extended from up to 6 years to up to 10 years therefore giving a longer period of MARKETING EXCLUSIVITY). It is estimated that more than 1,000 drugs had already been designated as o.d., with about 70 having a marketing authorization. In US, drugs for diseases affecting more than 200,000 subjects may receive orphan drug status if there is no reasonable expectation that the costs of developing and making available in the US a drug for such disease or condition will be recovered in the US; in most countries, APPLICATION FEES can be waived or are considerably reduced for o.d.; in some countries, there are also tax reductions as incentives. It is often possible to obtain o.d. designation also for diseases with a prevalence greater than that defined by the respective legislation if medically justifiable subgroups of patients (e.g. paediatric subsets) can be defined that fulfil the cut-off limit; usually, only one single drug receives o.d. status for a given market; see also EXPANDED-ACCESS PROGRAM, MARKETING AUTHORISATION, PREVALENCE RATE.

orthomolecular medicine Form of medicine that seeks to prevent diseases by balancing nutritional components and FOOD SUPPLEMENTS ("the right molecules in the right amount"); see also ALTERNATIVE MEDICINE, COMPLEMENTARY MEDICINE, FUNCTIONAL FOOD, INTEGRATIVE MEDICINE, PHYTOMEDICINES.

outcome measurement syn. outcome VARIABLE; see AGE-SPECIFIC RATE, ENDPOINT, PHARMACOECONOMICS.

outcomes research Research into health behaviour that reveals best medical practice based on evidence (EVIDENCE BASED MEDICINE); see also DISEASE MANAGEMENT, OUTCOME MEASUREMENT, QUALITY OF LIFE, REGISTRY, SURROGATE.

outliers DATA that have been incorrectly recorded (in contrast to out-of-range values); usually all data which are out of a range of twice the STANDARD DEVIATION are carefully looked at; care must be taken that only true errors in measurement are removed in order to rectify any data; as a rule of thumb only one o. may be excluded for each group of 40 samples, otherwise the method should be suspect; data are checked by examining the frequency DISTRIBUTION for impossible or outlying values; doubtful o. should be subject of a blind review process; see also DATA, ERRORS, FRAUD, RAW-DATA.

out-of-range values Data that have been correctly recorded but are outside of the expected (or normal) range; see also DATA, ERRORS, FRAUD, RAW-DATA.

outpatient Patient who is not hospitalized for treatment (opp. INPATIENT); considerable ingenuity is necessary in the design and execution of outpatient studies to circumvent typical difficulties as e.g. observations at less frequent intervals requiring substantial retrospection on the part of the patient, less tight control for intake of interfering medications or compliance with prescription, higher rates of DROP-OUTS, a.s.o.; some of the difficulties may be overcome by utilisation of PATIENT REPORT FORMS.

overdose see ADVERSE REACTION, DEFINED DAILY DOSE, SIGNIFICANT OVERDOSE.

overhead Regular expenses needed to operate a business, including the costs of rent, utilities, up-keep,, and taxes.

over-the-counter (OTC) syn. non-prescription DRUG; according to the EC, drugs are available without any prescription unless they are likely to present a RISK if used without medical supervision, are frequently and to a wide extent used incorrectly, contain substances requiring further investigation, or are normally prescribed by a doctor to be administered parenterally; OTC drugs are generally recognized as safe and effective; they are often used for self-medication; see also CONTROLLED DRUG, GENERAL SALE LIST MEDICINES, GRAS-LIST, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE, SELF-MEDICATION.

overweight see WEIGHT.

P

package insert see PATIENT INFORMATION LEAFLET; see also DEVELOPMENT SAFETY UPDATE REPORT, SUMMARY OF PRODUCT CHARACTERISTICS.

packaging EC (IV): "all operations, including filling and labelling, which a BULK PRODUCT has to undergo in order to become a FINISHED PRODUCT"; see also QUARANTINE.

packaging material EC (IV): "any material employed in the packaging of a MEDICINAL PRODUCT, excluding any outer packaging used for transportation or shipment; packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product".

packaging system syyn. Container closure system, (US): "sum of packaging components that together contain and protect the drug substance".

package leaflet see PATIENT INFORMATION LEAFLET.

pairing see MATCHED PAIRS, RANDOMISATION.

paper trail Integrity of the documentation record which allows a monitor or inspector to follow the process of events and confirm that the correct procedures were followed.

paradox see PETO'S PARADOX, REGRESSION PARADOX, SIMPSON'S PARADOX.

parallel design see DESIGN.

parallel import Patented substances are supplied by the holder of the patent to low priced countries for their domestic needs, sometimes manufactured locally, and then reimported to the high price country of the originator,

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thus lowering it's revenues; see also FALSIFIED MEDICINAL PRODUCT, MARKETING EXCLUSIVITY, PARALLEL TRADE, PATENT PROTECTION.

parallel track policy As part of an EXPEDITED DRUG DEVELOPMENT program trials without concurrent control group may be conducted in parallel with CONTROLLED CLINICAL TRIALS for collection of additional SAFETY and TOXICITY data; see also NON-COMPARATIVE TRIAL.

parallel trade Cross-border trade in parallel to the official supply chain of the manufacturer; parallel traders purchase the product in a low price country and resell it at higher prices in a high price country; the principle of free trade and the strictly regulated prices of medicinal products makes this legally possible; however there are quality concerns because products do not follow the intended supply chain; see PARALLEL IMPORT.

parametric test Statistical test assuming a defined distribution of the DATA, e.g. a NORMAL DISTRIBUTION.

parent–child/foetus report ICH: "Report in which the administration of medicines to a parent results in a suspected reaction/event in a child/foetus".

parenteral administration Opposite: enteral a.; see ADMINISTRATION.

Pareto's principle Also known as the "80:20 rule"; end of the nineteenth century, the Italian economist Vilfredo Pareto observed that 80 % of the land was owned by 20 % of the population; 20 % of the peapods in his garden produced 80 % of the peas, etc. and led to far-reaching theories; this principle has been applied to management as well, e.g., 80 % of the time of meetings is devoted to 20 % of the business, 80 % of the profit comes from 20 % of the sales; see also MUENCH'S LAW, MURPHY'S LAW, and LASAGNA'S LAW; see also MUENCH'S LAW, MURPHY'S LAW, and LASAGNA'S LAW, PAROUZZI PRINCIPLE, PERUSSEL'S LAW.

Parouzzi principle "Given a bad start, trouble will increase at an exponential rate"; see also MURPHY'S LAW, PARETO'S PRINCIPLE, PERUSSEL'S LAW.

partition coefficient Ratio of concentration of a substance in the lipid phase to the concentration in the aqueous phase when the substance is allowed to come to equilibrium in a two phase system; is a measure of lipid solubility of a DRUG; determines the uptake under un-ionised conditions; see also ABSORPTION, PHARMACOKINETIC, pKa.

password aging FDA 21CFR11 requests that "identification code and password issuances are periodically checked, recalled, or revised".

past medical history Especially important for chronic DISEASES; see also PATIENT FILE.

patent protection Most nations of the western hemisphere permit protection of patent for a period of 20 years after the date of filing; a complete description of the matter for which a patent is thought is required; the responsible agency in the US is the United States Patent and Trademark Office/USPTO (any person who "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent"), in the EC, the European Patent Office/EPO; see also CENTRALISED PROCEDURE, MARKETING EXCLUSIVITY, INTERNATIONAL BIRTH DATE, PARALLEL IMPORT, TRADEMARK.

pathogen Disease-causing organism.

patient see SUBJECT.

patient diary syn. patient report form; form on which patients record their subjective observations concerning a treatment; sometimes used in OUTPATIENT studies; as many as 89 % of all paper diaries may be either back- or forward-filled by patients; see also CASE RECORD FORM.

patient entry card Card which is sent by the investigator to the sponsor or CONTRACT RESEARCH ORGANISATION as soon as a new patient has been recruited.

patient exposure 100 patients exposed for a minimum of 1 year is considered to be acceptable as part of the safety data base for a NEW DRUG APPLICATION (ICH E1A); see also EXPOSURE DATA.

patient file File containing demographic and medical information about a patient, subject or volunteer (e.g. hospital file, medical record, consultation record, special subject file); such files are necessary for the verification of the authenticity of the information presented in the CASE REPORT FORM; they can be completed or corrected when new information is obtained.

patient identification list see SUBJECT IDENTIFICATION CODE LIST.

patient information leaflet (PIL) syn. see MEDICATION GUIDE, PACKAGE LEAFLET, PACKAGE INSERT, PATIENT PACKAGE INSERT, PATIENT PRODUCT INFORMATION; provides general information for patients on the correct use of a drug written in language easily understood; in most countries PILs are compulsory and controlled by the health authorities; contents and texts are different between PILs for patients and SUMMARIES OF PRODUCT CHARACTERISTICS for doctors.

patient information sheet As part of the INFORMED CONSENT process an information sheet can be handed out to the patient participating in a trial; this sheet summarizes the information given to the patient on the particular study; see also INFORMED CONSENT.

patient log book see SUBJECT IDENTIFICATION CODE LIST.

patient log list see SUBJECT IDENTIFICATION CODE LIST.

patient numbers see SAMPLE SIZE ESTIMATION.

patient package insert (PPI) see PATIENT INFORMATION LEAFLET.

patient product information (PPI) Information on pharmaceutical products, such as PATIENT PACKAGE INSERTS or e.g. the annually published Physician's Desk Reference; see also PATIENT INFORMATION LEAFLET.

Patient Protection and Affordable Care Act see CONFLICT OF INTEREST.

patient register see PATIENT IDENTIFICATION LIST, REGISTRY.

patient reporting see DIRECT PATIENT REPORTING.

patient report form (PRF) see PATIENT DIARY.

patient screening log see INTENT-TO-TREAT LIST, SUBJECT SCREENING LOG.

patient support program (PSP) Program (normally organized and funded by a pharmaceutical company) where patients and health care providers are supported concerning a particular treatment primarily with information but also with coverage and REIMBURSEMENT support on the authorised indication(s); the aim is usually to collect additional data on safety via spontaneous reports regardless of the cause (a NIS would collect data on both safety and efficacy, a PASS on safety, a PAES on efficacy and all of them use a protocol and provide financial compensation to physicians for their work); see also NON-INTERVENTIONAL STUDY (NIS), POST-AUTHORISATION EFFICACY STUDY (PAES), POST-AUTHORISATION SAFETY STUDY (PASS), POST-AUTHORISATION STUDY.

PDCA-cycle abbr. plan-do-check-action cycle; activities in clinical development are frequently done according to this scheme, where e.g. the clinical development plan is followed by the conduct of the study, the quality assurance step and finally by actions of management.

peak to trough concentration Ratio of peak concentration of a drug to it's average concentration; used for characterising properties of slow release formulations; see FORMULATION.

Pearson correlation coefficient see CORRELATION COEFFICIENT.

pediatric investigation plan (PIP) Granted by the EMA for medical products that are intended for paediatric usage (age <18 years). This plan intends to ensure that all necessary data are obtained in studies in children to support the

authorization of a medicine in children; see PEDIATRIC POPULATION, PAEDIATRIC-USE MARKETING AUTHORISATION.

pediatric population Population between 0 and 18 years (definition in the European Union); according to the ICH guideline E11, age groups of p.p. are the following: (i) preterm newborn infants <36 weeks gestation; (ii) term newborn infants 0–27 days; (iii) infants and toddlers 28 days – 23 months; (iv) children 2–11 years; (v) adolescents 12–16 or 12–18 years, depending on regions; see CONSENT, AGE GROUPS, GERIATRIC EVALUATIONS, PEDIATRIC INVESTIGATION PLAN, PEDIATRIC-USE MARKETING AUTHORISATION.

Pediatric-use marketing authorisation (PUMA) Marketing authorization by the paediatric regulation. PUMAs can be requested for medicines that are already authorized, not covered by intellectual property rights or exclusively developed for children. The PUMA covers indication and formulation of the medicines for usage in the PEDIATRIC POPULATION; see also PEDIATRIC INVESTIGATION PLAN.

penalities see BLACK LIST, SANCTION.

percentile range Interval between two specified percentile points, e.g. the inner 90 % RANGE includes all values between the 5th and the 95th percentiles, the inner quartile range values between 25th and 75th percentiles; the MEDIAN is the 50th percentile point; see also DISTRIBUTION.

performance assessment OECD: "Formal review of a system at periodic intervals to ensure that it continues to meet stated performance criteria, e.g. reliability, responsiveness, capacity"; see also ISO 9000, PHARMACEUTICAL QUALITY ASSURANCE, QUALITY CONTROL, TOTAL QUALITY MANAGEMENT.

performance indicators Measures for quality, e.g. time to report a SUSAR, to detect/correct deficiencies, number of deficiencies, number of missing data in a data set, ratio of critical/major/minor observations in an audit etc.; see also QUALITY CONTROL.

performance status syn. ECOG- performance status, scale after Zubrod; WHO 5-grade ORDINAL SCALE for describing characteristics esp. of tumour patients whereby: 0 = able to carry out all normal activity without restriction, 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; 2 = ambulatory and capable of all selfcare but unable to carry out any work up and about more than 50 % of waking hours; 3 = capable of only limited self-care, confined to bed or chair more than 50 % of waking hours; 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair; see also KARNOFSKY PERFORMANCE STATUS, QUALITY OF LIFE SCALE, RESPONSE. see also

ISO 9000, PHARMACEUTICAL QUALITY ASSURANCE, QUALITY CONTROL, TOTAL QUALITY MANAGEMENT.

Grade	ECOG-Zubrod description	Index (%)	Karnofsky description
0	Normal physical activity; not requiring special care	100	Normal, no complaints
		90	Able to carry on normal activities; minor signs or symptoms of disease
1	Slightly restricted physical activity; light work possible; not bedridden	80	Normal activity with effort
		70	Cares for self; unable to carry on normal activity or to do active work
2	Incapable of working; mostly independent conduct of life; requires special care and support; bedridden for <50 % of normal day;	60	Requires occasional assistance but able to care for most of his needs
		50	Requires considerable assistance and frequent medical care
3	Cannot care for self; continuous care or hospitalisation; bedridden for >50 % of normal day;	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalisation indicated though death not imminent
4	Bedfast due to disease	20	Very sick; hospitalisation necessary; active support treatment necessary
		10	Moribund
		0	Dead

periodic benefit-risk evaluation report (PBRER) Report acc. ICH E2C(R2) that replaces the PSUR; the benefits of a MEDICINAL PRODUCT must continuously outweigh the RISKS; in the US, the respective (not identical) documentation is called "Risk Evaluation and Mitigation Strategies" (FDA); see PERIODIC SAFETY UPDATE REPORT (PSUR).

periodic drug safety update report see PERIODIC SAFETY UPDATE REPORT.

periodic safety update report (PSUR) syn. DRUG SAFETY UPDATES; ICH-E2C: "report which presents the worldwide safety experience of a medicinal product at defined times post-authorisation, in order to (i) report all the relevant new information from appropriate sources, (ii) relate these data to patient exposure, (iii) summarise the market authorisation status in different countries and any significant variations related to safety, (iv) create periodically the opportunity for an overall safety reevaluation, (v) decide whether changes

should be made to product information in order to optimise the use of the product; … the marketing authorisation holder should submit a PSUR within 60 days of the data lock point; … the COMPANY CORE DATA SHEET with it's latest CCSI (numbered and dated) should be appended to the PSUR"; most regulatory authorities (e.g. EC) request regular collection of ADVERSE DRUG REACTIONS (foreign and domestic, at both pre- and post-marketing stages) and periodic updates concerning risk assessment of marketed products in order to maintain registration; according to recommendations of the working group of the COUNCIL FOR INTERNATIONAL ORGANISATIONS OF MEDICAL SCIENCES, in EC countries such PSURs should be periodically prepared, within 60 calendar days of the DATA LOCK-POINT, for all NEW CHEMICAL ENTITIES licensed for the first time in 1992 and thereafter; reports should be prepared for all authorised medicines at the following intervals: 6-monthly for the first 2 years after authorisation, annually for the subsequent 3 years (US: quarterly reports during the first 3 years, then annual reports; Japan: annually cohort surveys of a few thousand patients for 6 years, unlabeled non-serious AEs must be reported every 6 months for 3 years and annually thereafter), thereafter in 3- (former 5-) yearly intervals; regulatory aspects on safety update reports have repeatedly changed [1992 CIOMS II guideline published; 1996 ICH E2C guideline, step 4; 2003 ICH E2C (R1), step 4; 2012 ICH E2C (R2) step 3] and include now a formal evaluation of benefit (only for approved indications); consequently the name was changed to "Periodic Benefit-Risk Evaluation Report"; the scope is a (now cumulative) analysis of the risk-benefit balance; if the conditions of the MA are not fulfilled within the given deadline, the national competent authority has the power to "review" (suspend) the MA (Dir 2010/84/EC); in the EC, PSUR reporting is electronically directly to the EMA; the following information should be included: increased frequency of known origin, drug interactions, overdose and its treatment, drug abuse, positive and negative experiences during pregnancy or lactation, effects of long term treatment, any safety issues relating to special patient groups such as the ELDERLY or the very young; in contrast to the RMP which is cumulative, in the past, each PSUR covered just the time since the last PSUR (whereas the PBRER is cumulative) and a PSUR was required even if the product was marketed with detailed line listings of individual cases (now no longer routinely required); routine PSUR reporting (PBRER) can be "waved" under some circumstances, i.e. for products with a low risk or for old or for established products, unless concerns arise (e.g., "WELL ESTABLISHED USE", "TRADITIONAL HERBAL MEDICINAL PRODUCT", homeopathic, GENERICS); PSUR and PBRER may still be requested by the authority at any time; frequency of PSURs after (voluntary) withdrawal of a product from the market is decided by the CA on a case-by-case basis as there are no fixed rules; if a medicinal product is marketed by more than one company in member states of the EC, DATA LOCK POINTS can be harmonised

(http://www.hma.eu/uploads/media/PSUR_Work_Sharing_List_June_2009.pdf); see also ADVERSE EVENT, BENEFIT-RISK ANALYSIS, CESSATION OF PLACING ON THE MARKET, COMPANY CORE SAFETY INFORMATION, DATA LOCK-POINT, DEVELOPMENT SAFETY UPDATE REPORT, DRUG SAFETY UPDATES, EUROPEAN MEDICINES AGENCY, EXPOSURE DATA, INDIVIDUAL CASE SAFETY REPORT, INTERNATIONAL BIRTH DATE, LITERATURE SEARCH, PHARMACOVIGILANCE, PSUR SUMMARY BRIDGING REPORT, RENEWAL, RISK MANAGEMENT PLAN, TRANSITION MATRIX.

periodic site visit syn. routine monitoring visit; usually the MONITOR or CLINICAL RESEARCH ASSOCIATE visits the trial site every 4–8 weeks, with more frequent visits at the beginning of a trial; this frequency depends also on the intervals of controls scheduled in the PROTOCOL; all visits or contacts with the trialist have to be documented in order to comply with good clinical practice; see MONITOR'S VISIT LOG.

per-protocol analysis syn. Valid case a.; only patients finishing the study according to the protocol, without major protocol violations, are analysed, DROP-OUTS and WITHDRAWALS are excluded; opp. INTENT-TO-TREAT ANALYSIS; see also ANALYSIS OF STUDY RESULTS, MULTIPLE IMPUTATION APPROACH, VALID CASE ANALYSIS.

personalised medicine Treatment tailored to an individual patient (e.g., considering his age, weight, gender, medical history, …) or to a very small group of patients sharing a specific genetic particular; the Personalised Medicine Coalition defines p.m. as "the application of genomic and molecular data to better target the delivery of healthcare, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition"; e.g., about 4 % of patients with cystic fibrosis have the so-called G551D mutation; such patients have a defective protein that fails to balance the flow of chloride and water across the cell wall, leading to the build-up of internal mucus; this can be corrected (e.g., with Kalydeco®); see also ADVANCED THERAPY, BIOBANK, CYTOCHROMES P450, DISEASE MANAGEMENT, GENETIC VARIANCE, GENOME, NAIROBI PRINCIPLES.

Perussel's law "There is no job so simple that it cannot be done wrong"; see also MURPHY'S LAW.

pesticides There are about 30 endocrine disrupting pesticides used for growing fruits and vegetables (www.disruptingfood.info/); hormone-mimicking chemicals (endocrine disrupting chemicals, EDCs, e.g., DDT, bisphenol A, mancozeb) can be absorbed by the skin or ingested with food and interfere with the endocrine system of wildlife such as frogs but also humans; mancozeb is a

powerful, multi-active carcinogen. As EDCs are also used in the production of cosmetics, toys, shampoos, plastic components etc. their ubiquitous presence is a major threat to biodiversity worldwide and contribute to the extinction of species; see ALIMENTARY RISKS, EFSA.

Peto's paradox The incidence of cancer should be proportional to the number of cells and the number of cell divisions resp. the length of life; however, no correlation is found between cancer and [body size]×[longevity]; see also REGRESSION PARADOX, SIMPSON'S PARADOX, TELOMERE.

pharmaceutical benefit manager (PBM) Middleman in the US system, concentrating on the control of prescription medicines via drug lists, prices and also pharmacy procedure.

pharmaceutical company The oldest ph.c. in the world is Tanabe Seiyaku, established in 1678 in Japan, the oldest in Europe is Bayer, established in 1863, the oldest in the US is Procter & Gamble, established in 1837.

pharmaceutical equivalent syn. chemical e.; dosage form containing the same active ingredient(s) in the same amount(s) but possibly different inactive ingredients, while still meeting standards of a pharmacopoeia; see also THERAPEUTIC EQUIVALENT.

pharmaceutical evaluation report (PER) Scheme for the mutual recognition of evaluation reports of pharmaceutical products by health authorities.

pharmaceutical expenditure Spending on medical goods, in particular pharmaceuticals; it covers spending on prescription medicines and self-medication ("OVER-THE-COUNTER PRODUCTS"), as well as other medical non-durable goods. It also includes pharmacists' remuneration when the latter is separate from the price of medicines. Pharmaceuticals consumed in hospitals are excluded. Final expenditure on pharmaceuticals includes wholesale and retail margins and value-added tax. In 2005, the pharmaceutical expenditure per capita, public and private, was (US $, OECD, Health at a glance 2007): Austria 409, France 554, Germany 498, Italy 509, Japan 449, Norway 398, Spain 517, Switzerland 436, US 792; see DRUG CONSUMPTION, HEALTH CARE EXPENDITURE, MEDICAL CULTURE.

Pharmaceutical Inspection Convention (PIC) Provides exchange of such information between members (to date more than 15 mainly European health authorities) as is necessary for a member importer to recognise inspections carried out by the authorities in the member country where the drugs are manufactured (information about standards of manufacture as GOOD MANUFACTURING PRACTICE, control of drug products to be imported a.s.o.).

Pharmaceutical Manufacturers Association (PMA) Nonprofit scientific, professional, and trade organization consisting of more than 140 firms engaged primarily in the manufacture of prescription pharmaceutical, medical device, and diagnostic products; these firms account for more than 90 % of US industry sales of human dosage drugs; globally, by 2002 the 10 largest drug firms accounted for 48 % of pharmaceutical sales worldwide (1985: 20 %); 8 of 10 are the product of mergers since 1989; see MANUFACTURER.

pharmaceutical market The value of worldwide p.m. was valued in 2012; see also RESEARCH AND DEVELOPMENT.

pharmaceutical medicine IFAPP: "Medical scientific discipline concerned with the discovery, development, evaluation, registration, monitoring, and medical aspects of marketing of medicines for the benefit of patients and the public health".

pharmaceutical quality assurance EC: "the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use"; see also QUALITY ASSURANCE.

Pharmaceutical Research and Manufacturers of America (PhRMA) Represents the leading pharmaceutical industry research and biotechnology companies in the US.

pharmacodynamic Science dealing with the (pharmacologic) mechanism of drug action once it reaches the target organ(s); (relationships between the concentration of a drug at its site(s) of action and the magnitude of the biological or physiological effect that is achieved); primary ph. studies are studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target (in contrast to secondary ph. studies); see also PHARMACOKINETICS.

pharmacoeconomic study see ECONOMIC ANALYSIS.

pharmacoepidemiology Science of systematic or observational studies of DRUG EFFECTS in populations receiving the drug through usual clinical practice; objectives are, e.g., to detect unrecognised risks especially after long term administration and under widening conditions of use; p. includes the following main types of studies: prescription (utilisation) studies, which verify to what extent clinicians follow official recommendations and therapeutic indications stated e.g. by SUMMARIES OF PRODUCT CHARACTERISTICS FOR DOCTORS; studies on the therapeutic benefit, and studies of risk dealing with two main aspects: identification of events, and imputability of specific effects to the use of a given drug (still taking into account effects and interactions which might have been caused by concomitant treatments as well as by the natural course of DISEASES as e.g. concerning exposure, outcome, BIAS, CONFOUNDING, generalizability,

statistical stability a.s.o.); classical methods are: CASE-CONTROL-, COHORT-, CROSS-SECTIONAL STUDIES; see also POST-MARKETING-SURVEILLANCE.

pharmacogenetics Sometimes used synonymously with PHARMACOGENOMICS; science studying genetic response to a drug and people with unusual metabolism, thus inter-individual variations; see also CYTOCHROMES P450, ETHNIC DIFFERENCES, ICH E15 GUIDANCE, IDIOSYNCRATIC REACTION, METABOLISM, PHARMACOGENOMICS, PERSONALISED MEDICINE, SINGLE NUCLEOTIDE POLYMORPHISM.

pharmacogenomics Sometimes used synonymously with PHARMACOGENETICS; science studying the identification of the genes that influence individual variation in the efficacy or toxicity of therapeutic agents, thus on an individual level of gene-expression, and the application of this information in clinical practice; science studying genetic basis for diseases such as the correlation between genes, phenotypes and diseases; currently only the function of about 2,000 genes is known out of the potential of 100,000; see also ETHNIC DIFFERENCES, GENE THERAPY, GENOMICS, ICH E15 GUIDANCE, METABOLISM, PHARMACOGENETICS.

pharmacokinetic Science dealing with the disposition of DRUGS in the body [absorption, distribution, metabolism, and excretion (ADME)], in contrast to PHARMACODYNAMICS (actions of a drug); usually conducted as single dose studies or STEADY STATE STUDY; population pharmacokinetics takes into account that drugs behave differently in different populations, e.g. children or old persons; see also AREA UNDER THE CURVE, BIOAVAILABILITY, CLEARANCE, FIRST-PASS EFFECT, HALF LIFE, KINETIC, PARTITION COEFFICIENT, PROTEIN BINDING, VOLUME OF DISTRIBUTION.

pharmacokinetically guided dose escalations (PGDE) Dose escalation strategy in PHASE I oncological trials; it is based on the hypothesis that the area under the plasma concentration-time curve (AUC) at the LD-10 in mice and at the MTD in man are similar (patient's AUCs must be measured and be available rapidly); see also CONTINUOUS REASSESSMENT METHOD (CRM), DOSE ESCALATION, FIBONACCI SEARCH SCHEME, MAXIMUM TOLERATED SYSTEMIC EXPOSURE (MTSE).

pharmacology Science dealing with effects of a drug on organs or body systems; this covers the mutual interaction of chemical agents and biological systems, the nature of the action (i.e., the nature of the altered bodily response), the site of action, and the mechanism involved.

pharmacopoeia Regularly updated information on drugs in book form (standards of quality specifications such as purity, identity a.s.o.); quality of commercialized MEDICINAL PRODUCTS must comply with these standards; examples:

British P., British Homoeopathic P., US P., European P; the European P. has been elaborated by over 20 European countries including Member States of the European Community and has binding character, reinforced by EC directives.

pharmacovigilance (PV) Def.: "science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems" (WHO); "the process of monitoring, evaluating and improving the safety of medicines in use" (EMA); confounded sometimes with POST-MARKETING SURVEILLANCE; system for collecting (i) (passive surveillance) spontaneous REPORTS ON ADVERSE REACTIONS, assessing CAUSALITY and RISKS; major methods are: spontaneous, voluntary reporting schemes (e.g. YELLOW CARD system), or (ii) (active surveillance) such as intensive hospital monitoring, use of official statistics and observational, non-experimental studies such as CASE-CONTROLLED STUDIES, COHORT STUDIES, PRESCRIPTION-EVENT MONITORING, PRESCRIPTION SEQUENCE ANALYSIS; adverse reaction frequencies are expressed as cases per treatment or per month of treatment sold or per prescriptions; knowledge of drug sales is essential; although spontaneous reporting is the most commonly used method, whereby either the physician reports to the health authority (common in e.g. Austria, France, Italy) or the pharmaceutical company (Germany, USA); more and more countries accept reporting from patients/consumers ("consumer reports") in addition; before expansion of the PV legislation EMA estimated that adverse drug reactions cause about 197,000 deaths per year in the EU (population ~460 million) with 5,910 lives that can be saved by the more stringent laws [Commission of the European Community 10dec2008, Summary of the Impact Assessment, SEC(2008) 2671]; in comparison, TRANS FATS (components of many industrial foods) have been estimated in 1994 to have caused 20,000 deaths annually in the US from heart diseases (see also ALIMENTARY RISKS); acrylamide in food such as bread or other baked products or bisphenol A in plastic containers may be an even much greater problem; whereas PV activities of EMA were publicly funded in 2004 the have now to be paid by the pharmaceutical industry that has spent for meeting regulatory PV requirements an estimated € 833 million in 2008; one of the major drawbacks of PV is underreporting of events, causing underestimation, loss of statistical POWER and therefore erroneous conclusions; in some countries (e.g. France) a combined system of spontaneous reporting and semi-intensive hospital surveillance with regional centres is in use; retention of documents describing the PV system is requested for at least 5 years after it has ceased to exist, for PV-data and documents of authorized products at least 10 years after the end of MA; between September 2008 (after publication of Vol.9A) and June 2012 EMA has made public over 450 DIN A4 print pages regulating PV; see also BIAS, CONDITIONAL APPROVAL, DATA MINING, DRUG INJURY, DRUG SAFETY MONITORING, EUROPEAN MEDICINES AGENCY (EMA), INTENSIVE MONITORING, LITERATURE SEARCH, NUMBER NEEDED TO HARM, POST-AUTHORISATION

SAFETY STUDY, POST-MARKETING SURVEILLANCE, PRESCRIPTION-EVENT MONITORING, RECONCILIATION, REGISTRY, SAFETY OFFICER, SENTINEL SITES, SIMPSON'S PARADOX, SURVEILLANCE, YELLOW CARD.

pharmacovigilance system (Dir 2010/84/EC, Art.1, 28d): "system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance"; a PS should be subject o regular audits, i.e. "every 2 years"; see also PHARMACOVIGILANCE, PHARMACOVIGILANCE SYSTEM MASTER FILE, PHARMACOVIGILANCE SYSTEM SUMMARY, RISK MANAGEMENT SYSTEM.

pharmacovigilance system master file (PSMF) The PSMF should contain all elements related to PhV-activities, in particular information on the QP (CV, contact details, registration within the Eudravigilance system), description of the organizational structure (list of sites where PV activities are undertaken, collection of ICSRs, PSUR-generation, signal management, including on tasks delegated), description of computerized systems (incl. validation), data handling (continuous monitoring of the risk-benefit balance incl. decision process for taking appropriate measures, monitoring the outcome of risk-minimisation strategies), procedures for communicating safety concerns, description of the quality system (incl. training programs, reference to the location of qualification records); the PSMF should have an Annex containing the following documents: list of medicinal products covered by the PSMF, list of written procedures, list of outsourced/subcontracted activities, list of tasks delegated by the QPPV, list of completed and scheduled audits, if applicable list of PERFORMANCE INDICATORS, log list of changes of the PSMF; all documents should be indexed (Reg 520/2012 of 19 June 2012); (Dir 2010/84/EC): "A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products"; replaces the "DETAILED DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEM" as from July 2015 onwards and will receive a unique reference number; applications for marketing authorizations must include a reference where the PSMF is kept and available for inspections; where a pharmacovigilance system is shared by several marketing authorisation holders each MA authorisation holder is responsible ensuring that a PSMF exists to describe the pharmacovigilance system applicable for his products (GVP, Module II); the information on the PV system given herein is not confined just to local or regional activities; the PSMF contains, among others, also main findings of PV audits until resolution; the Member State in which the PSMF is located is also the respective supervisory pharmacovigilance authority (Reg 1235/2010); the competent authority may at any time ask for a copy of the PSMF (to be submitted within 7 days at the latest); see also DETAILED DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEM,

EUDRAVIGILANCE, PHARMACOVIGILANCE, PHARMACOVIGILANCE SYSTEM SUMMARY, SAFETY ALERTS.

pharmacovigilance system summary syn. Summary of the Pharmacovigilance System (SPS); "applications for marketing authorisations should be accompanied by a brief description of the corresponding pharmacovigilance system, which should include a reference to the location where the pharmacovigilance system master file for the medicinal product concerned is kept and available for inspection by the competent authorities" (Dir 2010/84/EU); further on, the summary may contain the most important elements of the PV system such as (see Dir 2001/83/EC Art.8(3)ia): company name + contact details + statement to fulfil the PV tasks, proof that the applicant has a QP-PV at his disposal, EEA Qualified Person(s) for Pharmacovigilance + contact details CVs + job descriptions, reference where the PSMF is kept; other information that may be included as requested by national authorities are: marketing authorization numbers of products/product list with INN + trade name(s) + method of approval (MA status) + black triangle (as applicable), safety variations/restrictions (as applicable), RMP, computerized systems/databases used, company structure/operating model for PV, 3rd party agreements/transfer of responsibilities, etc.; a PV system summary is not requested for traditional herbal medicinal products; see also PHARMACOVIGILANCE, PHARMACOVIGILANCE SYSTEM MASTER FILE, PHARMACOVIGILANCE SYSTEM, RISK MANAGEMENT SYSTEM.

pharmacy dispensing records List of experimental DRUGS dispensed by and returned to a pharmacy during a CLINICAL TRIAL; see also DRUG ACCOUNTABILITY.

pharmacy drug (P) Drug which can only be sold over the counter under the supervision of a pharmacist (UK); see also CONTROLLED DRUG, GENERAL SALE LIST MEDICINE, GRAS-LIST, PRESCRIPTION ONLY MEDICINES, OVER-THE-COUNTER.

phase 0 syn. microdose study; the purpose is to obtain preliminary data in humans, before commencement of a phase I study, with very small doses (not exceeding 100 μg or 100th of the predicted pharmacologic dose, whichever is smaller).

phase I First trials ("first-in-human", FIH) during clinical development of a new active ingredient in man, often in healthy volunteers; the purpose is to establish a preliminary evaluation of safety and a first outline of the PHARMACOKINETIC/-dynamic profile of the active ingredient in humans, associated with increasing doses (usually until an acute "effect" dose is reached), to permit the DESIGN of well-controlled, scientifically valid phase II studies; the total number of subjects is generally in the range of 20–80, the

mean development time 16 months (1987); commonly used target doses in phase I trials are e.g. the dose producing the "minimum anticipated biological effect" (MABEL, approach favourised by the EMA) or the "maximum recommended starting dose" (MRSD) based on the "no observed adverse event level" (NOAEL) determined in non-clinical toxicity studies in the most sensitive/most relevant animal species (FDA approach) or 1/3 of the TOXIC DOSE LEVEL (TDL) in the most sensitive large animal species, or 1/10 of the LD-10 (mg/m^2) in the mouse and 1/3 of the TDL in dogs, or 1/3 of the LD-10 in mice; target populations are usually healthy volunteers but may also be patients of the proposed indication such as cancer (for cytostatics), obese patients (for diabetics), HIV patients (for retrovirals), asthmatic patients (for bronchodilators) etc.; there are no clear regulations with regards to the number of individuals exposed; most frequently each dose level cohort consists of 6 subjects receiving the active medication and 2 receiving placebo whereby 3 subjects start (including 1 placebo) about 48 h before the rest of the cohort is exposed (staggered dosing approach); see also ADME, DOSE ESCALATION, FIBONACCI SEARCH SCHEME, LATIN SQUARE DESIGN, NOEL, TOXICITY TESTS.

phase II Therapeutic pilot studies; the purpose is to demonstrate biologic activity (often called phase IIa or early phase II) and later therapeutic effects (phase IIb, late phase II), in addition to short-term safety, of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended; the trials are performed in a limited number of subjects, usually some hundreds, and often, at a later stage, in a comparative (e.g. PLACEBO controlled) DESIGN; this phase also aims at the determination of appropriate dose ranges/regimens and (if possible) clarification of dose/response relationships in order to provide an optimal background for the design of wider therapeutic trials; the mean duration of phase II programs is about 24 months; see also GEHAN'S DESIGN, LATIN SQUARE DESIGN, ONE SAMPLE MULTIPLE TESTING DESIGN, PROOF-OF-CONCEPT.

phase III Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulations of the active ingredient, as well as to assess its overall and relative therapeutic value; the pattern and profile of more frequent ADVERSE REACTIONS must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences such as age etc.); the DESIGN of trials should preferably be randomized double-BLIND, but other designs may be acceptable for long-term safety studies; usually several hundred to several thousand subjects are included in MULTICENTRIC, often MULTINATIONAL studies; generally the circumstances of the trials should be as close as possible to normal conditions of use; the mean duration for a phase III program is about 36 months; trials performed after submission of a NEW DRUG APPLICATION are often called phase IIIb in contrast to earlier phase IIIa studies.

phase IV Investigations conducted, often as MULTICENTRE TRIALS, after approval of a new drug in approved indications, forms and dosages; def. EC: "studies performed after marketing of the final medicinal product(s), … according to the circumstances, phase IV studies require trial conditions (including at least a PROTOCOL) such as described for premarketing studies. After a product has been placed on the market, clinical trials exploring e.g. the profile vs new competitors, new methods of administration or new combinations, are considered as trials for new medicinal products"; EC guidelines subject therefore phase IV studies to the same controls as earlier clinical trials e.g. GOOD CLINICAL PRACTICE standards, INFORMED CONSENT, review by an ETHICAL COMMITTEE etc. (the FDA does not give a definition for phase IV); purposes of phase IV are e.g.: to delineate additional information about the drug's EFFECTIVENESS, benefits, risks, and optimal use (different doses or schedules) in special (sub)groups of patients, other stages of disease or use of the drug over longer periods of time, comparison with other drugs to assess therapeutic values (including safety, synergism/antagonism, COST/BENEFIT or QUALITY OF LIFE aspects), new treatment hypotheses or strategies a.s.o. including both experimental and OBSERVATIONAL (open label, uncontrolled) studies or simply to see how doctors actually prescribe the drug or how the drug works under non-trial conditions; term is often used interchangeable with the term POST-MARKETING SURVEILLANCE, but also for simple, non-blinded anecdotal, OBSERVATIONAL or promotional studies; trials exploring new methods of administration, new combinations, new indications etc. are considered within the EC as trials for new medicinal products; see also LARGE SIMPLE TRIAL DESIGN, NON-INTERVENTIONAL STUDY, POST-APPROVAL RESEARCH, POST-AUTHORISATION STUDY.

phenotype Literally means "the form that is shown"; the observed (physical) expression of the GENOTYPE of an organism, such as its morphology, development, biochemical or physiological properties, or behavior. Phenotypes result from the expression of an organism's genes as well as the influence of environmental factors and possible interactions between the two; this contrasts with the GENOTYPE of an organism (inherited instructions it carries within its genetic code). Not all organisms with the same genotype look or act the same way, because appearance and behaviour are modified by environmental and developmental conditions. Also in the same way, not all organisms that look alike necessarily have the same genotype; see also ALLELE, GENE, GENETIC VARIANCE, GENOME, GENOTYPE.

physical signature see DIGITAL SIGNATURE, ELECTRONIC SIGNATURE.

physician investigator Physician taking a dual role as researcher and investigator in academic studies; see NON-COMMERCIAL CLINICAL TRIAL, see also INVESTIGATOR, SPONSOR INVESTIGATOR.

phytochemical see PHYTOMEDICINE, see also HERBAL DRUG, HERBAL MEDICINAL PRODUCT.

phytomedicines syn. herbal medicines; medicines derived from plants; some health authorities review p. on the basis of single plants (e.g. Germany) as well as of combinations (e.g. France), other authorities on the basis of single products (e.g. UK); many health authorities have relaxed regulations for the submission of data on toxicity of phytomedicines as long as results of properly conducted clinical trials on efficacy and safety are submitted; in Europe, Germany is at present the largest market for p. covering about 70 % of the total consumption followed by France; within the EEC around 1,400 herbal drugs are used, roughly half of them are POM; about 25 % of OTC products are herbal medicines; see also ALTERNATIVE MEDICINE, FOOD SUPPLEMENT, FUNCTIONAL FOOD, HERBAL DRUG, ORTHOMOLECULAR MEDICINE, SELF-MEDICATION, TRADITIONAL HERBAL MEDICINAL PRODUCT.

phytonutrient see FUNCTIONAL FOOD.

pill-counting see COMPLIANCE.

pilot scale Manufacture of an ACTIVE INGREDIENT or of a finished product by a procedure that is representative for a full manufacturing scale; for solid oral dosage forms this is generally one-tenth that of a full production as a minimum or 100,000 units (tablets, capsules or the like); see BATCH.

pilot study syn. preliminary study, exploratory study; often performed to estimate treatment effects or RECRUITMENT RATES, to test out the practicability of new methods and the feasibility or suitability resp. of a PROTOCOL to a larger clinical project, in order to select the most suitable DESIGN and to ensure adequate recruitment; sometimes studies with a poor DESIGN are also called p.s. in order to avoid criticism; see also EXPLANATORY TRIAL, PIVOTAL STUDY.

pivotal data Data from CLINICAL TRIAL reports providing SUBSTANTIVE EVIDENCE of EFFICACY and safety on which a NEW DRUG APPLICATION can be judged; see also SUPPORTIVE DATA.

pivotal study Key study for primary evidence of efficacy; see also PILOT STUDY, SUPPORTIVE DATA.

pKa Negative logarithm of the acid dissociation constant; pH at which a substance exists half in ionised and half in the non-ionised form; pKa helps to predict ABSORPTION and whether EXCRETION of a substance can be increased by manipulating urinary pH (substances are more readily excreted in ionised form); alkalinisation of the urine with sodium bicarbonate can be used to hasten e.g. the excretion of phenobarbital and salicylates (acidification e.g. with

amphetamines is no longer recommended); see also ABSORPTION, ADME, ION TRAPPING, PARTITION COEFFICIENT, ROUTE OF ADMINISTRATION.

placebo Experimental preparation which has the same appearance as the active drug but which contains no pharmacologic active substance(s); a p. is normally not used when an established treatment, proven to be effective, is available and when the patient needs immediate treatment.

placebo effect Any effect(s) attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties; positive but also untoward p.e.s ("nocebo e.") can be observed in up to 40 % of patients with various symptoms e.g. pain; it's magnitude is influenced by a number of factors e.g. number of capsules, colour, taste etc.; patients (or family members) may mistakenly attribute events to the medication as opposed to the illness, just because they start to attend to symptoms that they previously denied or because of expectations; onset is almost immediately lasting up to several weeks; p.e.s and effects of a better general care, e.g. due to hospitalization ("hospitalization-effect"), are powerful sources of BIAS in medical research; see also BASELINE VARIABLE, CONFOUNDER, HAWTHORNE EFFECT, LABELLING PHENOMENON, REGRESSION PARADOX, WHITE-COAT HYPERTENSION.

placing on the market (EC): syn. actual marketing; "when a medicinal product is released into the distribution chain" and: "first making available in return for payment or free of charge of a medicinal product/device other than intended for clinical investigation, with a view to distribution and/or use on the Community market"; (regardless whether the device is new or fully refurbished); the MAH must notify the competent authority within 30 days of the (planned) initial placing on the market; see also LABEL TEXT.

plasmapheresis Nonselective removal of potentially harmful compounds from the plasma such as toxins by technical devices; see APHERESIS.

plasmid Extra-chromosomal genetic information in pro- and eukaryotes that can replicate independently of the chromosomal DNA and that can code for properties that provide a selective advantage under a given environmental state, e.g. antibiotic resistance; properties can be transferred "horizontally" between different species by conjugation; plasmids are responsible for multidrug-resistant strains of Gram-positive and Gram-negative bacteria, but also of Mycobacterium tuberculosis; see also GENE, GENETIC ENGINEERING, GENOME.

plasticity Ability of a cell to differentiate into many cell types (pluripotent) or a restricted cell line (multipotent); see also STEM CELL THERAPY.

plausibility check see DATA EDITING.

play-the-winner allocation If a treatment is followed by success, the next patient also receives this treatment; in case of failure the next patient receives the alternative treatment; only possible if results are known quickly (before recruitment of the next subject) and if hard ENDPOINTS are used; disadvantage: treatment allocation cannot be kept BLIND; see also RANDOMIZATION.

point estimation Estimation (calculation) of a single value of a more or less large sample of data – in contrast to interval estimates such as the confidence interval.

poisson shrinker see SIGNAL DETECTION.

polymerase chain reaction (PCR) A gene analysis technique used for enzymatic in vitro amplification of specific DNA sequences without utilizing conventional procedures of molecular cloning. It allows the amplification of a DNA region situated between two convergent primers and utilizes oligonucleotide primers that hybridize to opposite strands. Primer extension proceeds inward across the region between the two primers. The product of DNA synthesis of one primer serves as a template for the other primer; repeated cycles of DNA denaturation, annealing of primers, and extension result in an exponential increase in the number of copies of the region bounded by the primers. The process mimics in vitro the natural process of DNA replication occurring in all cellular organisms, where the DNA molecules of a cell are duplicated prior to cell division. The original DNA molecules serve as templates to build daughter molecules of identical sequence. Quantitative polymerase chain reaction (qPCR) is used for measuring the expression of genes of interest, monitoring biomarkers and measuring genetic variations (SINGLE NUCLEOTIDE POLYMORPHISM, SNPs).

polymorphism Variation in a DNA sequence present in an ALLELE FREQUENCY of >1 % in the population; see also ALLELE, GENETIC VARIANCE, GENOME, SINGLE NUCLEOTIDE POLYMORPHISM.

pooled analysis see META-ANALYSIS.

pooling of lab data In order to combine laboratory data from centres or studies with different reference ranges DATA must be converted; a simple method for standardization is to express data as multiples of the upper/lower reference value; more sophisticated methods are described by the following formula: new, standardised value = (old value – lower reference)/(upper reference – lower reference); if the lower limit is not specified it can be set 0; see also LABORATORY NORMAL RANGES.

poor metaboliser Subject lacking a specific enzyme because of alterations of the DNA; see also CYTOCHROME P450, ETHNIC DIFFERENCES, METABOLISM, PHARMACOGENETICS, SLOW METABOLISER.

population attributable risk see ETIOLOGIC FRACTION.

population pharmacokinetics see PHARMACOKINETIC.

positive list List of drugs reimbursable under a health insurance plan or offered under a capitated or managed care program or preferred in a particular clinical setting; such lists of medicines which are reimbursed by national healthcare or insurance systems resp, exist in a number of countries such as Belgium, Denmark, France, Greece, Italy, The Netherlands, Portugal and Spain; opposite: NEGATIVE LIST; see also DRUG LIST, NATIONAL FORMULARY, PRICE CONTROL, REIMBURSEMENT.

post-approval research (PAR) syn. post registration studies; studies on NEW CHEMICAL ENTITIES (NCE) requested by health authorities as a condition of approval and to define e.g. more clearly the incidence of known ADVERSE REACTIONS (ADR) in actual conditions of use (risk assessment studies), to look for unexpected ADR or to collect other important additional DATA, e.g. on BIOAVAILABILITY/-equivalence, drug/drug interactions, dosage a.s.o.; due to the absence of legislation, performing PAR is a "voluntary act" of the sponsoring firm; in USA 12–45 % of NCEs approved between 1970 and 1987 had PAR requests; between 1998 and 2003 the FDA required post-marketing commitments on 73 % of the drugs newly approved, the trend is increasing; see also CLUSTER RANDOMISED CONTROLLED TRIAL, LARGE SIMPLE TRIAL DESIGN, PHASE IV, POST-MARKETING SURVEILLANCE, REGISTRY.

post-authorisation study (PAS) Any study conducted within the conditions of the approved SUMMARY OF PRODUCT CHARACTERISTICS or under normal conditions of use; a PAS may sometimes also fall within the definition of PASS or PAES but can also be a phase IV study; see: NON-INTERVENTIONAL TRIAL, OBSERVATIONAL STUDY, PATIENT SUPPORT PROGRAM, POST-APPROVAL RESEARCH.

post-authorisation efficacy study (PAES) A PAES may be imposed by health authorities when "the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly" (Dir 2010/84); see also CONDITIONAL APPROVAL, POST-APPROVAL RESEARCH.

post-authorisation safety study (PASS) syn. post-marketing safety study; EC: "formal investigation conducted (in accordance with the terms of the MARKETING AUTHORIZATION) for the purpose of assessing the clinical safety of marketed medicine(s) in routine clinical practice; any study of a marketed medicine which has the evaluation of clinical safety as a specific objective"; the study must be such that the numbers of patients to be included will add significantly to the existing safety data; a PASS is "any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or

quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures" (Dir 2010/84); it can be NON-INTERVENTIONAL or INTERVENTIONAL in nature; Regulation (EC) 726/2004 states that "for a period of 5 years", but this period is unlimited in newer regulations; Reg. 1235/2010 states "at the time of marketing authorization or later following the initial placing on the market in the Community the Agency may request that the MAH arrange for specific pharmacovigilance data to be collected from targeted groups of patients"; see: ADDITIONAL MONITORING, CONDITIONAL APPROVAL, OBSERVATIONAL STUDY, PATIENT SUPPORT PROGRAM, PHARMACOVIGILANCE, POST-APPROVAL RESEARCH, POST-MARKETING SURVEILLANCE, SOLICITED REPORT, SURVEILLANCE.

post-marketing commitment (PMC) see: POST-APPROVAL RESEARCH.

post-marketing observational study see: OBSERVATIONAL STUDY, POST-APPROVAL RESEARCH.

post-marketing safety study see POST-AUTHORISATION SAFETY STUDY.

post-marketing surveillance (PMS) syn. drug monitoring, PHARMACOEPIDEMIOLOGY; involves the collection of clinical data on marketed medicines, primarily on drug safety (incidence of esp. rare side effects, new hazards, specific risk factors, risk/benefit analysis) but also on unexpected benefits, and their scientific evaluation or cost/benefit aspects, and to evaluate if drugs are prescribed as directed; often the approach is retrospective which might then cause severe bias; surveillance can be "passive", i.e. spontaneous reporting of ADRs to National Authority, Event Monitoring, ICSR, or "active/solicited", i.e. as studies by industry or academic institutions (safety follow-up, ph IV, OBSERVATIONAL st., "sentinel"sites, PRESCRIPTION-EVENT monitoring, …); true PMS technique should tap the results of field use of a medicine without disturbing prescribing decision or patient selection; for marketing, PMS provides therefore information on the performance of the drug in general use, often on the base of automated RECORD LINKAGE rather than in data sheet use, and may be an alternative to MEGATRIALS or long-term follow-up; in some EC member states, e.g. Austria, Belgium, France, Germany, Ireland, PMS studies may be a condition of marketing approval (RESTRICTED MARKETING AUTHORISATION) and required by health authorities (POST-APPROVAL RESEARCH); in Australia PMS study proposals should be notified to the ADRAC-APMA; in some countries (e.g. US) PMS is also required for MEDICAL DEVICES such as permanent implants, devices which are intended for use in supporting or sustaining human life or which present a potential serious RISK to health, especially when failure occurs; see also INDIVIDUAL CASE SAFETY REPORT, NON-ALPHA SITE, NON-INTERVENTIONAL TRIAL, PHARMACOVIGILANCE, REGISTRY, SURVEILLANCE.

potency see: STRENGTH.

powder inhaler DRUG DELIVERY SYSTEMS which are specifically designed for the delivery of drugs to the lungs, either using a dose premetered at the factory (metered and dispensed in a sealed unit) or a volumetric metering system which is activated by the patient for every dose; particles must be in the respirable range of <5.8 μm; see also DRUG DELIVERY SYSTEMS, FORMULATION.

power Statistical term for 1-b; probability of avoiding a type II (BETA) ERROR; chance of obtaining a significant result if the real effect is as great or greater than the smallest worthwhile difference (DELTA VALUE) specified; typical choices are powers of 90 or 80 %; see also SAMPLE SIZE CALCULATION.

practice effect see SEQUENCE EFFECT.

pragmatic analysis see INTENT-TO-TREAT ANALYSIS.

pragmatic/decision-making trial Trial where only the superiority of one treatment over the other (A > B) is important, not equality; see also EXPLANATORY TRIAL, LARGE SIMPLE TRIAL DESIGN.

precision Often used synonymously to REPEATABILITY and VARIABILITY; p. of a method is expressed by the STANDARD DEVIATION of repeated measurements, obtained under identical conditions; when deviation is high, results are widely scattered and measurements are imprecise; see also ACCURACY, MEASUREMENT PROPERTIES.

preclinical safety see ADVERSE REACTION, S-2 REPORT.

predicted environmental concentration (PEC) – If the PEC of a medicinal product is ≥0.01 μg/L surface water an ENVIRONMENTAL RISK ASSESSMENT must be performed.

predictive marker Intended to forecast how patients may respond to a treatment agent. Often linked to tumour sensitivity or resistance to a medical intervention. Molecular markers may have both prognostic and predictive implications, as the human epidermal growth factor 2 (HER2) in breast cancer; see also BIOMARKER, PROGNOSTIC MARKER.

predictive value Proportion of those patients with a positive (negative) test who are diseased (not diseased), see also SENSITIVITY, SPECIFICITY.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Evidence-based minimum set of 27 items for reporting in systematic reviews and meta-analyses.

preferred term (PT) see medDRA, WHO ADVERSE REACTION TERMINOLOGY.

pregnancy see LABELLING, VULNERABLE SUBJECT, WOMEN.

pregnancy outcome End products of pregnancy which include three main categories: foetal death, termination of pregnancy and live birth.

preinvestigation visit see PRESTUDY VISIT.

prelicensing agreement (PLA) Equivalent of a NEW DRUG APPLICATION by the Center for Biologic Evaluation and Research (US).

premarketing trial see PHASE IIIB.

premarketing agreement (PMA) Equivalent of a NEW DRUG APPLICATION by the Center for Devices and Radiological Health (US).

premature termination EU: Termination of a clinical trial before the (planned) end has to be communicated to the relevant health authorities within 15 days, including the reason for early termination; see also DROP-OUT, LOSS TO FOLLOW-UP, WITHDRAWAL.

premedication Medication taken till start of therapy with a study DRUG.

prescription see MEDICAL CULTURE, OVER-THE COUNTER, PHARMACEUTICAL EXPENDITURE, PRESCRIPTION ONLY MEDICATION.

prescription-event monitoring (PEM) Multiple COHORT scheme, cohort-event monitoring; technique collecting (in contrast to spontaneous reporting) actively DATA from field use of a medicine without disturbing prescribing decisions or patient selection; after introduction of a new medication, a defined number of patients, e.g., 10,000, is followed. Physicians prescribing the new medication are contacted and asked to report all observations (solicited report), regardless of whether they are suspected AEs (full data sets, anonymised) (common in UK); PEM is an accepted method for post-marketing surveillance although it may be biased by collecting data from clusters of patients (less likely for the broader "INTENSIVE MONITORING"); see also DRUG SAFETY MONITORING, PHARMACOVIGILANCE, SENTINEL SITES, SPONTANEOUS REPORTING SCHEME, YELLOW CARD SYSTEM.

prescription only medication (POM, Rx) (UK) syn. ethical drug, prescription-drug, prescription medicine, general term: medicinal product (EC-term); opp. self-medication, non-prescription drug, OVER-THE-COUNTER (OTC); drug which can only be received in a pharmacy and with a prescription of a physician; see also CONTROLLED DRUG, GENERAL SALE LIST MEDICINE, GRAS-LIST, PHARMACY DRUG, SELF-MEDICATION.

prescription-sequence analysis (PSA) Technique to assess quickly the extent of the risk of side effects of marketed drugs; investigates whether patients

treated with the drug under review have sequentially started on a different therapy to treat the reported side-effect; PSA is possible only when the adverse reaction at issue causes the prescribing of other drugs and if complete dispensing records from health maintenance organisations or insurance systems are available; also useful to detect "DRUG CHANNELLING".

prescription study see PHARMACOEPIDEMIOLOGY.

preservatives Substances (e.g. alcohols, benzalkonium chloride, chlorocresol, thiomersal) included in pharmaceutical FORMULATIONS to inhibit the growth or kill micro-organisms inadvertently introduced during manufacture or use; see also ANTIOXIDANTS, DISINTEGRANTS, EXCIPIENTS, FORMULATION.

prestudy documentation syn. pretrial documentation; before a study can start the following documents must be available: protocol incl. appendices (as e.g. the case record forms, consent forms, patient information sheet) authorisation to conduct the clinical trial, approval by the responsible ethics committee(s), curriculum vitae of all participating trialists, contract with the trialists, laboratory normal ranges, insurance.

prestudy meeting syn. INVESTIGATORS meeting, START-UP meeting; especially in MULTICENTRE trials, the MONITOR has not only to make sure that investigators and their staff have understood the PROTOCOL and the issues of the study but also that methods of assessments are harmonised (e.g. ORDINAL SCALES or other subjective measurements).

prestudy visit syn. preinvestigation visit, pretrial visit; visit to a potential trial centre in order to explore if prerequisites to conduct a CLINICAL TRIAL are met (numbers of patients, manpower, equipment, competing trials, experience of the trialist a.s.o.); according to GOOD CLINICAL PRACTICE such visits have to be documented; see also INITIATION VISIT.

presystemic hepatic elimination see FIRST-PASS EFFECT.

pretreatment phase see RUN-IN PHASE.

pretrial data EC (III): "chemical, pharmaceutical, animal pharmacological and toxicological data on the substance and/or the pharmaceutical form in question must be available and professionally evaluated before a new product is subject to CLINICAL TRIALS; the SPONSOR's responsibility for providing exhaustive, complete and relevant material, e.g. by means of an INVESTIGATOR'S BROCHURE, is emphasized".

pretrial documentation see PRESTUDY DOCUMENTATION.

pretrial visit see PRESTUDY VISIT.

prevalence rate def.: number of subjects, at a single point in time, with a specific attribute (disease) divided by the total number of subjects (total population); the p. of a disease can change over time (e.g. HIV infections); see also AGE-SPECIFIC RATE, CASE-FATALITY RATE, DIAGNOSTIC INDEX, INCIDENCE RATE, NEYMAN FALLACY, ONSET-ADJUSTED INCIDENCE RATE, ONSET-ADJUSTED PREVALENCE, ORPHAN DRUG, PREVALENCE.

prevention trial see INTERVENTION TRIAL.

price control Prices of medicinal products are controlled by almost all health authorities; products must have their own realistic prices, calculated on the basis of their real costs and using transparent methods of calculation; a number of governments have introduced pricing controls and cost-containment measures such as NEGATIVE/POSITIVE LISTS, PROFIT CONTROLS (PRICE REGULATORY SCHEME), REFERENCE PRICING, the right for substitution of doctor's prescription by a cheaper (generic) product by the pharmacist (e.g., The Netherlands) or simply price cuts; see also HEALTH CARE COSTS, PRICE REGULATORY SCHEME, REIMBURSEMENT.

price regulatory scheme (PPRS) prices of medicinal products are heavily but not uniformly regulated; in UK, voluntary agreement between the governmental Department of Health (DoH) and the industry association (ABPI) to limit national health spending on pharmaceuticals; the principle of this scheme is to control overall profitability of pharmaceutical companies as measured by the return on capital (ROC) which is set to be between 17 and 21 %; companies which fall below their target of ROC by 25 % or more are eligible to apply for a price increase, those exceeding the upper limit by 25 % must either pay back the excess to the DoH or reduce the prices; the PPRS caps also selling and promotion expenditures to 9 % and information expenditures to 1.6 % of overall sales; see also HEALTH CARE COSTS, REFERENCE PRICING, REIMBURSEMENT.

primary endpoint Also called key data, key (efficacy) criteria; variable used for SAMPLE SIZE CALCULATION; usually hard endpoints, objective endpoints; outcome VARIABLES which are considered as especially important for postulating a clinically meaningful difference (death, stroke, reinfarction, time to relapse, infection rate etc. or biological markers specific for the underlying disease as e.g. antigen levels, which can be used as SURROGATE endpoints); ideally they should also be easy to measure with both precision and accuracy, and clearly important to the patient; an alternative, multi-dimensional approach to a unique primary endpoint are "co-primary endpoints" that must all be statistical significant; examples for statistical tests for multiple endpoints are the "WEI-LACHIN" procedure or the modified "O'BRIAN" test.

priming dose see LOADING DOSE.

principal investigator (PI) see INVESTIGATOR.

prion Postulated since 1969, but unproven causative agent of transmissible spongioform encephalopathies (TSE), such as Creutzfeld-Jakob disease (CJD) in humans (a rare ORPHAN DISEASE affecting about 1/1 Mio people), bovine spongioform encephalopathy (BSE) in cattle (transmissible to man), and scrapie in sheep; see also CONTAMINATION, SECONDARY ATTACK RATE.

PRISMA Stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses; evidence-based minimum set of items for transparent reporting in systematic reviews and META-ANALYSES (http://www.prisma-statement.org/statement.htm); see also PUBLICATION GUIDELINES, REPORT

probability see SIGNIFICANCE LEVEL.

procedures EC: "description of the operations to be carried out, the precautions to be taken and the measures to be applied directly or indirectly related to the manufacture of a MEDICINAL PRODUCT".

process owner (senior) manager of a process; see also SYSTEM OWNER.

prodrug Pharmacologically inactive form of a drug in an oral pharmaceutical FORMULATION; after contact with intestinal secretions the active form is released by splitting of chemical bonds; e.g. ester-groups in bacampicillin (prodrug of ampicillin, an antibiotic) or ramipril (an ACE-inhibitor); prodrugs have in general a better BIOAVAILABILITY than the parent substances and therefore less gastrointestinal side effects.

production EC: "all operations involved in the preparation of a MEDICINAL PRODUCT, from receipt of materials, through processing and packaging, to its completion as a FINISHED PRODUCT".

product see DRUG, ESSENTIALLY SIMILAR PRODUCT, PROPRIETARY MEDICINAL PRODUCT, THERAPEUTIC EQUIVALENT.

product defect Defects of a medicinal product that are neither potentially life threatening or nor a serious risk to health ("class 3 defect", e.g., missing batch number or expiry date); see also QUALITY DEFECT, PRODUCT RECALL.

product information Overall term for the SUMMARY OF PRODUCT CHARACTERISTICS, PACKAGE INSERT and LABELING; see also QRD-FORMAT.

product liability EC (I): the producer of a medicinal product "shall be liable caused by a defect in his product"; "the injured person shall be required to prove the damage, the defect and the causal relationship between defect and

damage"; in the EC, pl applies to a lack of safety and not to the fact that a product is not fit for the intended use; the responsibility to pay for damages is placed on the producer; see also COMPENSATION FOR DRUG INDUCED INJURY, INDEMNIFICATION, INSURANCE, QUALITY DEFECT.

product license (PL) Approval to advertise, supply and sell a MEDICINAL PRODUCT; products that have been granted a license carry a number beginning with the letters PL on the manufacturer's pack.

product license application (PLA) European term for application for marketing authorisation; see also ESTABLISHMENT LICENCE APPLICATION, NEW DRUG APPLICATION.

product-limit method see KAPLAN–MEIER METHOD.

product monograph see REFERENCE SAFETY INFORMATION.

product quality review (PQR) regular (annual) review of a licensed medicinal product or active pharmaceutical ingredient verifying the consistency of the existing manufacturing process; see also GOOD MANUFACTURING PRACTICE, PRODUCT SPECIFICATION (FILE).

product recall A firm's removal or correction of a marketed product to avoid legal action (e.g., seizure); the manufacturer must implement a system for recalling and reviewing complaints together with an effective system for recalling promptly and at any time the medicinal products in the distribution network; recalls are classified (FDA, EU) into class I to III according to the relative health hazard (risk of death i.e. patient-level recalls (I), to (II) defect may be harmful but not life-threatening, and (III) "not likely to cause adverse health consequences". The MHRA also issues "Caution in Use" Notices which are called a Class 4 Drug Alerts, where there is no threat to patients or no serious defect likely to impair product use or efficacy. These are generally used for minor defects in packaging or other printed materials (http://www.mhra.gov.uk/home/groups/islic/documents/publication/con007572.pdf). The categories define also the depth of recall/level in the distribution chain to which the recall is to extend (wholesaler, retailer, user/consumer); over the years, the number of product recalls shows an upward trend in almost all categories of products; see also <www.recalls.gov>, <www.info.rasmas.nobilis.org>, WITHDRAWAL.

product specification file EC: "reference file containing all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping"; the product specification consists of a list of tests, the related analytical procedures and the acceptance criteria; the PSF contains also STABILITY data and relevant technical agreements with contract givers.

prognostic marker Foresees in an objective and independent manner the clinical outcome of a patient such as e.g., patients at risk of relapse or with an overall bad prognosis.

programmatic error A medical incident that was caused by some ERROR in transportation, storage, handling or administration of vaccines.

program evaluation technique (PERT) syn. network chart; program management technique which uses statistical probabilities to calculate expected durations of activities; today it refers mainly to the graphic representation of task relationships or dependencies in a project.

project management Stresses that priorities are set, that schedules are rigidly adhered to, that specifications are clear, and that activities are carefully monitored; examples of major p.m. techniques are the CRITICAL PATH METHOD (CPM), PROGRAM EVALUATION TECHNIQUE (PERT), GANTT chart, WORK BREAKDOWN STRUCTURE (WBS), Pareto chart, fishbone chart a.s.o.

project plan As a program or functional plan it should contain the following information: long-term goal that should be reached, objectives specifying precisely the "what and when" of intended accomplishments, strategies based on resource statement of personnel, equipment, and facilities required, and what program evaluation will be set up (input/output measure, work-load m., benefit m.).

project book note see TRIAL MASTER FILE.

prolonged release syn. extended r., slow r., sustained r.; a product in which the rate of release of active substance from the formulation after administration has been modified (reduced) in order to maintain therapeutic activity over a longer period, to reduce toxic effects, or for some other therapeutic purpose (European Pharmacopoeia, EudraLex 3AQ19a: Quality of prolonged release oral solid dosage forms, Nov. 1992; FDA Guidance for the industry, http://www.fda.gov/cder/guidance/index.htm); it may or may not be CONTROLLED RELEASE; see also DELAYED RELEASE, DISSOLUTION TEST, DRUG DELIVERY, TRANSDERMAL PATCH.

promoter see SPONSOR.

promotional trial see MARKETING TRIAL.

proof-of-concept syn. Proof-of-principle; proof that a new treatment, based on hypotheses and/or preclinical results; is working in man (usually during PHASE II); see also RESEARCH & DEVELOPMENT.

proportion The numerator contains a subset of the individuals contained in the denominator; see also RATE.

proportional reporting ratio see DISPROPORTIONALITY ASSESSMENTS, SIGNAL DETECTION.

proprietary medicinal product (PMP) opp. GENERIC.

proprietary name see TRADE NAME.

prospective study Trial in which subjects are documented and monitored in accordance with a protocol which has been set-up before recruitment; opposite: restrospective study; see also CLINICAL TRIAL.

protected subjects see VULNERABLE SUBJECT.

protein Proteins are biological effector molecules encoded by an organism's genome. A protein consists of one or more polypeptide chains of AMINO ACID subunits. The functional action of a protein depends on its three dimensional structure, which is determined by its amino acid composition and any post-transcriptional modifications; see also PROTEIN BINDING.

protein binding Many drugs bind to plasma proteins but only the unbound fraction is available for diffusion to the site of action; drugs with a high p.b. have a small VOLUME OF DISTRIBUTION; they do not easily penetrate the cerebrospinal fluid and are also not easily removed by extracorporeal dialysis; acidic substances bind to albumin, basic substances to alpha-1-glycoprotein; p.b. can be affected by diseases (e.g. hypoalbuminaemia increases the unbound fraction) but also by comedication (displacement of a drug by another drug which binds stronger); see also PHARMACOKINETIC.

proteomics The development and application of techniques used to investigate the protein products of the genome and how they interact to determine biological functions; science of "proteoms" i.e. looking at the entire set of proteins, protein structure and function of an organism; applications are in the identification of disease markers for diagnose (BIOMARKER) and drug targets; see also GENE, GENOMICS, GENE THERAPY.

protocol syn. study plan, (clinical) investigational plan; a document or manual of operation resp. which states the rational, objectives, statistical design, methodology etc. of a trial, with the conditions under which it is to be performed and managed; EC (III): "The p. must, where relevant, contain the following … items: general information, justification and objectives, ethics, general time schedule, general design, subject selection, treatment, assessment of efficacy, adverse events, practicalities, handling of records, evaluation, statistics, financing,

reporting, approvals, insurance, etc., summary, supplements, references"; the protocol can define those serious ADVERSE REACTIONS that do not request immediate reporting; see also DEVELOPMENT SAFETY UPDATE REPORT, PRE-TRIAL DATA; for other types of documents see ANNUAL PROGRESS REPORT, REFERENCE SAFETY INFORMATION, see also ADDENDUM, AMENDMENT.

protocol deviation Usually minor non-compliances with the protocol in contrast to PROTOCOL VIOLATIONS.

protocol violation Usually major deviations from a protocol in contrast to PROTOCOL DEVIATIONS.

protopathic bias Exposure to a drug occurs in response to a symptom of a disease undiagnosed at the time of exposure [erroneous conclusion that exposure to a drug caused the (later diagnosed) disease]; example: use of an analgesic in response to pain (caused by an undiagnosed tumour at the time of prescription) could lead to the conclusion that the analgesic caused the tumour; see BIAS.

PSUR Summary Bridging Report No longer required since ICH E2C(R2), 2012; report bridging all PSURs (ICH E2C(R1); Vol.9A: "the PSUR Summary Bridging Report should not contain any new data but should provide a brief summary bridging two or more PSURs, or PSURs and PSUR Addendum Reports. PSUR data should not be repeated but cross-referenced to individual PSURs. The format should be identical to that of the usual PSUR but the content should consist of summary highlights and an overview of data from the attached PSURs"; see also DEVELOPMENT SAFETY UPDATE REPORT, PERIODIC BENEFIT-RISK EVALUATION REPORT.

publication guidelines See the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/); see also ACKNOWLEDGEMENTS, AUTHORSHIP AUTHORSHIP, CONSORT (Consolidated Standards for Reporting Trials), EQUATOR NETWORK (http://www.equator-network.og), MOOSE (reporting of Meta-analyses Of Observational Studies in Epidemiology), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); REPORT, STARD (STAndards for the Reporting of Diagnostic accuracy studies), STROBE (STrengthening the Reporting of Observational studies in Epidemiology).

public health emergency A "natural disaster" that poses "a high probability of a large number of deaths" or harm to a population; WHO: A public health emergency (the condition that requires the governor to declare a state of public health emergency) is defined as "an occurrence or imminent threat of an illness or health condition, caused by bio-terrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin, that poses a

substantial risk of a significant number of human facilities or incidents or permanent or long-term disability" (WHO/DCD, 2001). The declaration of a state of p.h.e permits to suspend state regulations and change the functions of state agencies; http://www.who.int/hac/about/definitions/en/; this definition would also include the appearance of a novel of previously controlled or eradicated infectious agent, a natural disaster, a chemical attack or accidental release, or a nuclear attack or accident AND an incident that poses a high probability of a large number of deaths in the affected population, a large number of serious or long-term disabilities in the affected population, or widespread exposure to an infectious or toxic agent that posses a significant risk of substantial future harm to a large number of people in the affected population.

pulse pressure Difference between systolic and diastolic blood pressure; ideally below 50 mmHg; see also MEAN ARTERIAL BLOOD PRESSURE.

p-value (p) Chance of obtaining the observed result or one more extreme if one assumes that the effects of the treatments are equal; p is therefore the confidence with which the NULL-HYPOTHESIS is rejected and not the confidence with which one accepts that the difference is exactly zero; if $p = 0.05$, the null-hypothesis is rejected with a probability of 5 % and one accepts that the effects are different, or, the other way round, we accept an error rate (of falsely rejecting the null-hypothesis) of 1 in 20 cases; non-significant p-values only imply that the data remain consistent with the null-hypothesis of treatment equality and not that equivalence has been demonstrated (!); see also ALPHA ERROR, CONFIDENCE INTERVAL, POWER.

pyrogenicity test see LIMULUS AMEBOCYTE LYSATE TEST.

Q

qualification EC (IV): "action of proving that any equipment works correctly and actually leads to the expected results; the word VALIDATION is sometimes widened to incorporate the concept of qualification"; (operational qu., installation qu., performance qu., …).

qualified person (QP) In order to be eligible for manufacturing authorization pharmaceutical firms must employ the following key personal: a production manager, a qualified person for batch release, a control manager (responsible for quality control/drug testing), a sales manager; companies distributing medicinal products must have a Qualified Person PHARMACOVIGILANCE (QPPV); they may be the same person in special cases; proof of the expert knowledge is generally requested; see also BATCH RELEASE, GOOD MANUFACTURING PRACTICE, EUDRAVIGILANCE, QUALITY CONTROL, RELEASE CERTIFICATE.

qualitative variable see DATA.

quality-adjusted life-years (QALY) syn. healthy-year equivalent (HYE); QALYs are calculated by multiplying the time spent in each health state by the value assigned to the particular health state; to calculate QALYs, numerical judgments of the desirability of various outcomes must be determined; these values are called "utilities" (with values between 0-death and 1-perfect health); very poor health states may have even negative values; see COST/UTILITY ANALYSIS.

quality assurance (QA) EC (III): "systems and processes established to ensure that a trial is performed and the DATA are generated in compliance with GOOD CLINICAL PRACTICE including procedures for ethical conduct, STANDARD OPERATING PROCEDURE (SOP), reporting, personal qualifications etc.; this is validated through inprocess quality control and in- and post-process auditing, both being applied to the CLINICAL TRIAL process as well

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as to the DATA"; "personal involved in q.a. AUDIT must be independent of those involved in or managing a particular trial"; (inhouse) q.a.-personal is in general responsible for identifying q.a. problems, recommending and providing solutions and for verifying implementation of such solutions (e. g. ensuring and validating systems concerning training, SOPs, development planning, ETHICS COMMITTEE review, regulatory review, internal approvals, monitoring, auditing a.s.o.); the existence of q.a.-units is not required by current regulations; see also ISO 9000, PHARMACEUTICAL QUALITY ASSURANCE, QUALITY CONTROL, TOTAL QUALITY MANAGEMENT.

quality assurance profile Computerised information system used by the FDA to track the compliance status of all drug and medical device manufacturers, repackers, relablers, contract testing laboratories and contract sterilizers; see also INSPECTION.

quality control Operational techniques and activities to ensure that a process (e.g., a clinical trial) is in compliance with the principles of "GXP" (i.e. GOOD CLINICAL PRACTICE for clinical trials); it operates upon all members of the respective team (e.g., the investigational team with clinical staff, SPONSOR, CONTRACT RESEARCH ORGANISATION etc.) involved with planning, conducting, monitoring, evaluating, and reporting a process (trial) including DATA processing and documentation or the effectiveness of corrections, with the objective to establish and protect the credibility of activities and generated data, to improve the ethical, scientific and technical quality (e.g., of a trial), to avoid loss of information, false conclusions being drawn from unreliable data and to avoid at the very end exposure of subjects to unnecessary risks; elements of q.c. are e.g. SOURCE DATA VERIFICATION, DATA TRAIL, internal and external AUDITS but also quality objectives and PERFORMANCE INDICATORS (e.g., time to detect/correct deficiencies, number of deficiencies); q.c. applies to all processes such as PHARMACOVIGILANCE or the MANUFACTURE but also to analytical processes of MEDICINAL PRODUCTS; q.c. is therefore comparable to the "monitoring" of clinical research, whereas QUALITY ASSURANCE compares with the "auditing" of clinical research; see also PERFORMANCE ASSESSMENT, QUALIFIED PERSON, QUALITY SYSTEM, STANDARD OPERATING PROCEDURES.

quality defect a medicinal product has a "quality defect" if this defect is potentially life threatening or could cause serious risk to health ("class 1 defect", e.g., higher concentration of an active ingredient or "class 2 defect", e.g., chemical/physical contamination); defects that are not class 1 or class 2 defects are PRODUCT DEFECTS; in most cases this will induce a batch recall; see also COMPENSATION FOR DRUG INDUCED INJURY, FALSIFIED MEDICINAL PRODUCT, PRODUCT LIABILITY, REPROCESSING.

quality of life (QL, QoL) Def. (WHO): "an individual's perception of his/her position in life in the context of the culture and values system in which he/she lives, and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept, incorporating in a complex way the person's physical health, psychological state, and level of independence, social relationships and their relationship to salient features of their environment"; QL instruments may relate the use of healthcare resources to various aspects of the improved WELL-BEING of patients; main components of QL assessments are: physical and occupational functions (functional capacities), psychological state, emotional life and social interaction, and somatic sensation; this definition is therefore based on both subjective (SYMPTOMS, general well-being) and objective judgments (SIGNS, WELFARE as duration of hospitalisation, need for assistance, amount of drugs used a.s.o.); especially important for marketed products which: extend life only at the expense of reduction in QL (e.g. in oncology), when the disease itself causes little complaints in contrast to treatments chosen to prevent complications (e.g. hypertension, diabetes type II), when treatment is life-long but therapeutic gain, if any, small, when assessment of improvement of QL may be the best way of demonstrating the efficacy of a medicine, and when a regulatory authority has to make difficult decisions relating to the balance of benefit and risk of a new medicine; in Japan QL data will become a formal criterion for anticancer drugs, in France QL (and COST/EFFECTIVENESS) data are explicit criteria for determining prices and REIMBURSEMENT; major instruments for QL assessments are: QUALITY OF LIFE SCALES, HEALTH PROFILES, UTILITY MEASUREMENTS and specific, disease-oriented measurements; methods are e.g. LINEAR ANALOGUE SELF ASSESSMENT, time without symptoms, TIME TRADE-OFF etc.; besides the clinical perspective QL has also an economic perspective: UTILITY MEASUREMENT; see also COST/BENEFIT ANALYSIS, HEALTH-RELATED QUALITY OF LIFE, HEALTH UTILITIES INDEX, LIFE EVENT, PERFORMANCE STATUS, WELL-BEING SCALE.

quality of life scale Examples are: generic instruments such as the SF-36 (generic QL instrument, 36 item short form of the Medical Outcome Study MOS-20/MOS-9), Sickness Impact Profile (SIP, esp. for more healthy people), Nottingham Health Profile (NHP), or more specific instruments such as the Spitzer's Quality of Life Index (QLI, for patients with cancer and chronic diseases), Incapacity Status Scale (ISS), Profile of Mood States (POMS), Psychological General Well-Being Index (PGWB, for the emotional domain of quality of life), KARNOFSKY PERFORMANCE STATUS, EORTC Quality of Life Questionnaire (EORTC-QLQ), Environmental Status Scale (ESS), Anamnestic Comparative Self Anchoring Scale (ACSA, where the patient describes the current situation with reference to her/his best or worst life time on a scale ranging from −5/worst to +5/best), a.s.o.

quality of life studies Three study designs are commonly used: (i) a cross-sectional or non-randomised longitudinal design which describes predictors of QL (e.g. primary care vs. speciality) and where usually large numbers of patients (over 500/group) are needed; (ii) a randomised interventional study, where measures clearly reflect the nature of the disease and changes; (iii) a cost effectiveness or cost benefit analysis measuring incremental costs of a treatment program vs. incremental effects on health, e.g. measured as survival or quality adjusted life years; see also COST/EFFECTIVENESS ANALYSIS.

QRD format Standing for Quality Review of Documents; format requested in the EU for the PRODUCT INFORMATION (i.e. the SUMMARY OF PRODUCT CHARACTERISTICS).

quality system The organizational structure, responsibilities/tasks assigned, procedures (QUALITY CONTROL, training plans/records, records management, instructions for compliance and performance management), processes (identification of critical processes, quality audits), and resources for implementing quality management; see also STANDARD OPERATING PROCEDURES.

quantitative variable see DATA.

quarantine EC (IV): "the status of starting of PACKAGING MATERIALS, INTERMEDIATE, BULK or FINISHED PRODUCTS isolated physically or by other effective means whilst awaiting a decision on their release or refusal".

query log see DATA RESOLUTION FORM.

query resolution see DATA MANAGER.

query resolution form see DATA RESOLUTION FORM.

questionnaire see FORWARD-BACKWARD TRANSLATION, TEST-RETEST, VALIDATION.

Quetelet index syn. BODY MASS INDEX; Weight (kg) divided by the square of height (m); see also WEIGHT.

quorum Minimum number of members of an ETHICS COMMITTEE (usually five) which have to be present for a votum on a trial PROTOCOL.

Q-value Ratio of the improvement from baseline by the study drug divided by the improvement from baseline by the control drug; efficacy can be considered when a q-value exceeds 0.6; see also EFFECT SIZE, SAMPLE SIZE ESTIMATION.

R

racemate Equimolar mixture of ENANTIOMERS; see also CHIRALITY, STEREOISOMER.

racial differences see ETHNIC DIFFERENCES, GENOME.

radiopharmaceutical EC (I): "any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose"; for content of radioactivity, the deviation from that stated on the label should not exceed ±10 %.

randomization SUBJECTS are allocated to two or more treatments by mere chance; the aim of r. is that all potential confounders are roughly equally balanced between the treatment groups; appropriate r.methods are: computer generated random numbers, tables of random numbers, allocation in sealed (opaque!) envelopes; inappropriate are: allocation by date of birth or admission, identification number, initial letter of the subject's name, flipping coins, drawing cards etc. as such procedures do not allow any external control; the trialist is also not "BLIND", but can choose between subjects if they are present at the same time and may be seduced after e.g. a long series of treatment A to "modify" the process of chance etc.; in case of simple r. each treatment assignment is completely unpredictable (favourite procedure when treatment allocation cannot be kept blind); in CLINICAL TRIALS of finite size, simple r. however can end up with unequal treatment numbers (for a total number of 50 patients the probability for an imbalance as large as 18:32 is ≥0.05); it is often preferable to stratify patients prior to grouping them in order to avoid imbalances (r. within strata; see STRATIFICATION); for balancing numbers, esp. in case of small groups, it is often suitable to restrict randomization e.g. in random permuted blocks (restricted r., block r.); see also BLOCK SIZE, MINIMIZATION; in variable block r., a modified version of block r., the investigator does not know the number of patients to be recruited before balance is achieved (variable block sizes); it is advisable not to inform the investigator

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of block sizes; in the biased coin method one observes continuously which treatment has the least patients so far; that treatment is then assigned with a probability >1/2 (e.g. ¾) to the next patient; if little is known about a new treatment in contrast to a control treatment, esp. if this is PLACEBO, then unequal r. may be an attractive, case saving alternative (e.g. in PHASE II or rare diseases), whereby for every patient e.g. in the control group two patients are allocated to the new treatment; such a 2:1 allocation would be equivalent (in terms of POWER) to perform a 1:1 allocation and eliminating about 10 % of the patients from the trial; unequal r. should however not exceed a 3:1 ratio in order to avoid a considerable loss of power; a similar r. strategy is followed in the PLAY-THE-WINNER allocation; unequal r. might also be desirable when more than one treatment group is to be compared with a standard control, increasing the relative number receiving the CONTROL treatment; see also CONFOUNDER, RANDOMIZED CONSENT DESIGN, SQUARE-ROOT RULE.

randomization code Code according to which treatments are allocated to patients in a CONTROLLED CLINICAL TRIAL; under blinded conditions the TRIALIST must be able to break the CODE in emergency cases (serious ADVERSE EVENTS) in order to identify the treatment; usually codes for each patient are contained in separate envelopes; see also DISCLOSURE PROCEDURES.

randomized consent design Here, in contrast to the common procedure, RANDOMIZATION takes place before seeking INFORMED CONSENT of patients to treatment; this results apparently in three, rather than two groups: a standard treatment group as control (without consent) and the study group which is asked for consent to the new treatment; those patients not giving consent to the new treatment are ultimately combined with the CONTROL group mentioned previously; a prerequisite for the successful implementation of a r.c.d. is that the percentage of patients in the seek consent group and who accept the study treatment will be close to 100 %; such a DESIGN may be considered in surgical trials when it would be difficult to assign a patient at random to a more radical operation in comparison with e.g. a standard chemotherapy; ethical problems concerning the group "without consent" may however arise when protocols require e.g. invasive diagnostic or other procedures being not necessarily part of a "standard" treatment.

randomized controlled clinical trial see CONTROLLED CLINICAL TRIAL.

range Interval between the lowest and the highest value within a DISTRIBUTION of DATA; see PERCENTILE RANGE, STANDARD DEVIATION.

randomized withdrawal see DESIGN.

Rapid Alert (RA) Procedure primarily between health authorities; a RA is used when there are safety concerns which potentially have a major impact on the known BENEFIT-RISK balance of a medicinal product and which could

warrant prompt regulatory action and communication to Healthcare Professionals/the general public; examples: (i) URGENT SAFETY RESTRICTION, with important changes in the SUMMARY OF PRODUCT CHARACTERISTICS (SPC), e.g.: introduction of new contraindication, of new warnings, reduction in the recommended dose, duration or pack size, restriction of the indications; (ii) Restriction in the availability of a medicinal product; (iii) Need to inform Healthcare Professionals or Patients about an identified risk without delay and/or recall of the medicinal product from the market; (iv) Suspension of marketing and/or use of a medicinal product; all changes must be approved by the competent authority (CA) before implementation; see also SAFETY ALERT, URGENT SAFETY RESTRICTION.

rapporteur Original member state (REFERENCE MEMBER STATE or expert of a member state) within the EC, in which a marketing authorization for a medicinal product has been obtained according to the criteria laid down by the EC directives or first member state to which a HIGH-TECH PROCEDURE application (DECENTRALISED PROCEDURE application) has been addressed by a company or expert selected by the COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)/COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS (CVMP) or expert designated by national authorities; the r. notifies the CPMP of the application, prepares an evaluation report with questions, circulates it to all member states and the company, makes a compilation of all eventual objections (which are discussed/filtered by the appropriate working party and CPMP), and sends the resulting list of objections to the company and to all member states; after the answer of the company to all member states the r. collects again the conclusions on the answers to the questions raised and applies for the opinion of the CPMP; then the r. as well as the member states concerned notify the Commission of the European Community of their decision on the action to be taken following the opinion of the CPMP; if there were no serious objections the Commission would adopt a decision to implement the opinion of the CPMP, if there were objections the Council would reach a decision; if however no decision is reached by the Council after 3 months the application would be considered to have been rejected; see also DECENTRALISED PROCEDURE .

rare diseases see ORPHAN DISEASES.

rate A numerical statement of the frequency of an event, expressed in terms of person-time; differences and rates are common summary measures; see also PROPORTION.

rating scale Scale with a set of numerical categories; see SCALE.

raw data Records or certified copies of the original clinical, laboratory or other findings from the trial; electronic data must be in a "human readable format" i.e. in a format that everybody can read (e.g., converted to a standard format

such as .pdf; the process must be validated to ensure data integrity); term is sometimes used as a synonym for data in CASE RECORD FORMS; see also SOURCE DATA VERIFICATION.

reaction see ADVERSE REACTION.

reaction products see IMPURITY.

Read clinical classification (RCC) System using five character alphanumeric codes for codifying diseases, diagnoses, diagnostic procedures, examination findings, signs, symptoms, patients history, drugs, treatment, laboratory results, environmental and social conditions, administrative procedures, outcome and severity measurements within a hierarchical dictionary containing more than 30,000 terms.

rebound effect Reappearance of a sign or symptom that were present already before after abrupt WITHDRAWAL of a drug e.g. after stopping antihypertensive treatment with clonidine blood pressure may "overshoot" in rare cases.

recall see GMP, PRODUCT DEFECT, PRODUCT RECALL, QUALITY DEFECT, WITHDRAWAL.

recessive An allele whose effects are concealed in offspring by the dominante allele in the allele pair; see also ALLELE, DOMINANTE, GENE, HETEROCYGOUS, HOMOCYGOUS, RECESSIVE.

rechallenge Reappearance of an adverse reaction on repeated exposure (ethically justified only when benefits outweigh the risks); to avoid false positive r. tests due to PLACEBO EFFECTS or a flare-up of the disease immediately before, the r. must be carefully planned and performed; in contrast, a positive dechallenge reaction is an adverse event which disappears on withdrawal of the drug; see DECHALLENGE, SINGLE CASE EXPERIMENT.

rechallenge trial see DESIGN.

recombinant DNA technology see GENETIC ENGINEERING.

recommended daily allowances (USRDA) Values for vitamins and minerals, established by the FDA (US) for labelling purposes; see RECOMMENDED DIETARY ALLOWANCES.

recommended dietary allowances (RDA) values for vitamins and minerals, determined by the Food and Nutrition Board of the National Research Council (US); intake of the RDA will provide adequate nutrition in most healthy persons under usual environmental stresses; they are not minimum requirements; see RECOMMENDED DAILY ALLOWANCES; see also FOOD SUPPLEMENTS, ORTHOMOLECULAR MEDICINE.

reconciliation EC (IV): "a comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used"; in PHARMACOVIGILANCE the term is used to refer to the concept of ensuring that all appropriate information has been correctly identified, completed and transferred (e.g., between a clinical trial database and a separate safety database).

recordkeeping In USA records of a clinical trial have to be retained for a period of 2 years following the date on which: (a) the test article is approved by the FDA for marketing for the purposes which were the subject of the trial, (b) the entire trial is discontinued or terminated; records of INSTITUTIONAL REVIEW BOARDS must be kept for a minimum of 3 years after completion of the research; EC: retention of patient identification codes, patient files and other SOURCE DATA by INVESTIGATOR for at least 15 years, all relevant documentation by SPONSOR or subsequent owner for the lifetime of the product, the final report for 5 years beyond the lifetime of the product; archived data may be held on microfiche or electronic record.

record linkage System where all health data of an individual are recorded, from birth to death; source of information for PHARMACOVIGILANCE programs; see also ECOLOGICAL STUDY.

record retention see ARCHIVING.

recovery EC (IV): "the introduction of all or part of previous BATCHES of the required quality into another batch at a defined stage of MANUFACTURE".

recruitment period syn. inclusion period; period until the number of patients as planned in the protocol is included in the study.

recruitment rate syn. accrual rate; it is a common phenomenon (LASAGNA'S LAW, MUENCH'S LAW, MURPHY'S LAW), that as SOON as CLINICAL TRIAL starts, the number of available patients dramatically drops and increases again at the end of the study; reasons are e.g.: tight ELIGIBILITY CRITERIA, overestimation of patient numbers, impracticability of technical parts of PROTOCOLS, problems in obtaining INFORMED CONSENT a.s.o.; for counteracting, loosening of entry criteria, availability of INTENT-TO-TREAT lists, retrospective analyses of the number of suitable patients, and checks for ongoing suitability (facilities) of the centre are helpful, investigations and additional work for trialists should be kept to a minimum; complex protocols may require a precedent PILOT STUDY to ensure feasibility; (EC: "responsibilities of the INVESTIGATOR: to provide retrospective data on numbers of patients who would have satisfied the proposed entrance criteria during preceding time periods in order to assure an adequate recruitment rate"); emphasis should be put on detecting low r.r. early to allow timely adjustments.

recurrence risk see EMPIRIC RECURRENCE RISK, RISK.

recycling of a drug see LIFE CYCLE MANAGEMENT.

reference member state (RMS) syn. rapporteur; see also DECENTRALISED PROCEDURE, PRICE CONTROL, PRICE REGULATORY SCHEME.

reference pricing syn. fixed payment system; the patient is reimbursed a fixed amount of money (which is defined by the therapeutic class), irrespective of the selling price of the drug; such payment system exists in a number of countries such as Germany, The Netherlands, Denmark, Sweden and Belgium; see also PRICE CONTROL, PRICE REGULATORY SCHEME, REIMBURSEMENT.

reference range see LABORATORY NORMAL RANGE.

reference risk Risk in a population of unexposed subjects ("baseline/background risk"); for the purpose of comparisons, the characteristics should be as close as possible to the characteristics of the exposed population; see also RISK.

reference safety information (RSI) source on the safety of a product in particular relating to the expectedness and frequency of (serious) adverse reactions; the r.s.i. is commonly the safety information that is included in all current SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs) of the product (common denominator), as authorised in Member States at the time of DATA LOCK POINT; usually it is the COMPANY CORE DATA SHEET (CCDS) or the COMPANY CORE SAFETY INFORMATION (CCSI); other types of safety documents are: developmental core safety information (DCSI)/developmental core data sheet (DCDS), DEVELOPMENT SAFETY UPDATE REPORT, INVESTIGATOR'S BROCHURE, PATIENT INFORMATION LEAFLET, PERIODIC SAFETY UPDATE REPORT, product monograph; changes are to be described in the relevant section of the PSUR; see also ADVERSE REACTION.

reference sample syn. reference standard; (EU Guide to GMP) "A sample of a batch of starting material, packaging material, product contained in its primary packaging or finished product which is stored for the purpose of being analysed should the need arise"; where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, which are transported outside of the manufacturer's control, should be kept. In many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable. Reference and retention samples of investigational medicinal product, including blinded product should be kept (in a sufficient amount to permit at least two full analyses) for at least 2 years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer; they are also called secondary reference standards; primary reference standards may also be obtained from an officially recognised source; see also RETENTION SAMPLE.

reference standard see also REFERENCE SAMPLE.

regenerative medicine Treatment aimed to replace or regenerate human cells, tissues or organs to restore or establish normal function, e.g. by stem cells; see also STEM CELL THERAPY.

register see DATA BASE.

registry Basically a collection of data of patients with the same characteristics; e.g., a specific disease, condition or outcome (HIV, pregnancy, birth defects – "disease" registry) or the same treatment/exposure (drug registry, exposure r.; ICH E2E; www.effectivehealthcare.ahrq.gov); registries are repositories where data, records or laboratory samples are kept and may be made available for research or comparative studies. e.g., physicians/specialised institutions may maintain lists of patients who share a characteristic, such as a medical condition or medication regimen. Safety registries capture and document ongoing safety and outcomes data in patient populations under real-world treatment conditions; see also EPIDEMIOLOGY, OBSERVATIONAL STUDY, OUTCOMES RESEARCH, PHARMACOVIGILANCE, POST-APPROVAL RESEARCH, SURVEILLANCE.

regression coefficient see LINEAR REGRESSION.

regression paradox syn. regression toward the mean, statistical regression; spontaneous variations of symptoms or diseases make judgments of drug effects virtually impossible, e.g. a patient with recurrent headaches is most likely to seek medical help when his headaches are most severe or frequent; the spontaneous return to a baseline pattern would appear to be an improvement; if the patient is treated, this regression will create an appearance of drug efficacy even if, in fact, the drug is completely inactive; another example: an antihypertensive treatment seems to be more effective in severe hypertension (artifact of r.p.: the higher the blood pressure the further it can fall!); it is also more likely that an extremely high or low value is a measurement error which, when repeated, will be much closer to the intermediate; therefore tendency toward a less extreme repeat value is always greater than tendency for an intermediate value to become more extreme; regression to the mean is also a rationale for RUN-IN PHASES; see also BASELINE VARIABLE, PLACEBO EFFECT.

regression to the mean see REGRESSION PARADOX.

regulations – R. are legal acts that enable the European Community institutions to encroach furthest on the domestic legal systems in the EC; they lay down the same law throughout the Community, regardless of international borders, and apply in full in all Member States ("community character"); in contrast to DIRECTIVES the legal acts do not have to be transposed into national law but confer rights or impose duties on the Community citizen in the same way as national law; the Member States and their governing institutions and courts are

bound directly by community law and have to comply with in the same way as with national law ("direct applicability"); in contrast to guidelines, r. are legally enforceable; see DIRECTIVE, EC LAW.

reimbursement Treatment costs reimbursed by health insurance systems; for reimbursement, the price for a medicinal product must be permitted and is often compared to that of a competitor (e.g., for a new GENERIC) or an other comparably effective drug, sometimes also with the price on other comparable markets as a reference; see ANATOMICAL THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM, BLACK LIST, COPAYMENT, COST/BENEFIT ANALYSIS, COST/EFFECTIVENESS, DEFINED DAILY DOSE, NEGATIVE LIST, POSITIVE LIST, PRICE CONTROL, QUALITY OF LIFE, REFERENCE PRICING.

relational data base Special, structured d.b. whereby data are managed and stored with an a priori logical relationship between the data; see also DATA MANAGER.

relative bioavailability see BIOAVAILABILITY.

relative incidence Portion of subjects with a specific attribute (AR) versus the portion exposed (incidence proportion); see also CUMULATIVE INCIDENCE, EXCESS INCIDENCE, INCIDENCE RATE, PREVALENCE RATE.

relative risk see RISK.

release certificate Certificate documenting that adequate quality controls have been performed and that the investigational medicinal product has been released by a qualified individual (QUALIFIED PERSON) prior to being used in clinical trials; r.c. must be available in the TRIAL MASTER FILE.

reliability Usually determined by the extent that a SCORE has repeatability between identical or equivalent tests, therefore by: interperson r. = CONSISTENCY of scoring between different individuals, test re-test r. = consistency of scoring over a short period of time when subjects have not changed, and internal r. = correlation of individual items to the total score; see also MEASUREMENT PROPERTIES, VALIDITY.

remote data entry Capturing data at site where they are generated, e.g. at the investigational centre; the ELECTRONIC DATA can than be either stored locally and transferred later or can be transferred on-line; see also CLOUD SYSTEMS, COMPUTERISED SYSTEMS, DATA ENTRY, ELECTRONIC DATA CAPTURE, REMOTE DATA ENTRY, SOURCE DATA, WEB-BASED DATA ENTRY.

renewal Marketing Authorisations (MA) granted in the European Community have an initial duration of 5 years; at least 6 months (amended to 9 months for products for which the MA ceases after 21 Apr 2013 as by Reg 1235/2010) before the authorization ceases the MA holder must provide the competent

authority with a consolidated version of the file in respect of quality, safety and efficacy in order to maintain MA; once renewed the MA shall be valid for an unlimited period; see also MARKETING AUTHORISATION, SUNSET CLAUSE.

repeatability Level of agreement between replicate measurements made in the same subject; see also MEASUREMENT PROPERTIES.

repeated dose toxicity see TOXICITY.

repeated looks on data see INTERIM-ANALYSIS, MULTIPLE COMPARISONS.

repeated measures design D. with multiple measurement periods instead of simple pre-/post-evaluations; usually equal sample sizes at each measurement period and complex statistical techniques are needed (e.g. multivariate repeated measures analyses of variance).

repeated significance testing see BONFERONI CORRECTION, INTERIM-ANALYSIS, MULTIPLE COMPARISONS.

repeat study see REPLICATION STUDY.

replication study syn. repeat s.; additional study to a research question; some authorities require studies to be replicated in their country.

report Essential elements are e.g. summary: brief description (ca. 1 page) of the study objective(s), methods, main findings and general conclusions; introduction: with the main reasons for conducting this trial in the particular way; methods/subjects/patients: description of selection criteria, design, blinding, statistical methods etc.; results: with BASELINE comparison of treatment groups, number of subjects RANDOMIZED, COMPLIANCE (in case of outpatients) analyses of EFFICACY and SAFETY according to INTENT-TO-TREAT PRINCIPLE, number of subjects which might be excluded from analyses and reasons, estimation of (group) differences, P-VALUES, CONFIDENCE INTERVALS, evaluation of centre by treatment interaction (for MULTICENTRE TRIALS); discussion/conclusions: critical comparison with published or other existing information; a summary report is to be submitted to the competent authorities within one year of the end of the clinical trial; according to EC guidelines of good clinical practice (III) r. of clinical trials have to be archived 5 years beyond the life time of the product; detailed recommendations are found in the CONSORT checklist (CONSOLIDATED STANDARDS OF REPORTING TRIALS, http://www.consort-statement.org/consort-statement/); the checklist includes 25 items where empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect, or because the information is essential to judge the reliability or relevance of the findings; see also DEVELOPMENT SAFETY UPDATE REPORT, EXPEDITED REPORTING, FINAL REPORT, IMRAD, INTEGRATED REPORT, PARENT–CHILD/FOETUS REPORT, PERIODIC SAFETY UPDATE REPORT, PUBLICATION

GUIDELINES, S-2 REPORT, UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS.

reporting see PUBLICATION GUIDELINES.

reporting odds ratio see DISPROPORTIONALITY ASSESSMENTS.

reprocessing EC (IV): "the reworking of all or part of a BATCH of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations"; see also QUALITY DEFECT.

reproducibility Often used synonymously to PRECISION and VARIABILITY; extent to which the same result is obtained (or would have been obtained) when a measurement is repeated; the better the r. of MEASUREMENTS, the lower the STANDARD DEVIATION and therefore the VARIANCE; see also ACCURACY, MEASUREMENT PROPERTIES.

reproductive toxicity Toxic effects upon reproduction of mammals; studies investigate possible adverse effects of substances on male or female fertility and general reproductive performance ("segment I"), teratogenicity ("segment II"), and peri- or postnatal effects resp. such as physical and functional development in the offspring ("segment III"); see also GENOTOXICITY, LABELLING, TOXICITY TESTS.

reprofiling of a drug see LIFE CYCLE MANAGEMENT.

rescue medication Also called escape medication; medicines identified in a study protocol as those that may be administered to the patients when the efficacy of the investigational medicinal product (IMP) is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard (adverse reaction) to the patient, or to manage an emergency situation; see also INVESTIGATIONAL MEDICINAL PRODUCT.

research and development (R&D) The average NEW CHEMICAL ENTITY (NCE) that receives MARKETING AUTHORISATION may cost about 4–11 billion US$ (2012) taking into account research failures; in 2002 estimated costs were 802 million, in 1990: $ 231 million, and takes about 12 years, with little changes since 1987, from synthesis to marketing approval (about 3 years in the 1960s); this includes costs of failed projects and time costs (mean development times: long-term animal studies 3.5 years, phase I 1.5 years, phase II 2 years, phase III 3.5 years, NEW DRUG APPLICATION review by FDA 1.5 years); R&D expenditure (EFPIA) increased from € 7,766 mio (1990) to 27,796 million (2010) in Europe; during the same period regulatory requirements have tremendously increased; there are in addition regular costs after marketing authorisation, e.g. up to € 80.000 for the assessment of each PSUR; to bring 10 NCEs on the

market, it is estimated that researchers must evaluate 100,000 compounds of which companies can put about 100 products into clinical trials – but only two of the 10 NCE will be profitable for the discovering company; worldwide R&D expenses were about 49 billion US$ in 2004 and 68 billion in 2010 (after 15,000 million US $ in 1988, 24,500 million in 1992 and 33,700 million in 1995), with about 15–25 NCEs approved each year (35 in 1989); each additional week of clinical development accounts for a loss of sales revenues in the order of $ 1–10 million US $; worldwide ethical pharmaceutical sales were in the order of $ 400,000 in 2002 (112.000 million in 1988); R&D oriented companies expend about 10–20 % of their revenues for R&D and 20–30 % for marketing; see also CLINICAL DEVELOPMENT PLAN, DEVELOPMENT, HEALTH CARE COSTS, LIFE CYCLE MANAGEMENT, PHARMACEUTICAL MARKET, PROOF-OF-CONCEPT, STUDY LIST.

research coordinator see CLINICAL TRIAL COORDINATOR.

research nurse see STUDY NURSE.

reserve sample see RETENTION SAMPLE.

residues see IMPURITY.

response R. can be presented in different ways, e.g. as difference (value before – value after), as ratio (value after//value before), as percentage change [(value after/value before – 1) × 100], percentage of patients with a defined value at a given moment, a.s.o.

response (cancer treatment) For reporting results of cancer treatment the following definitions (WHO) of objective response are used (separately!): (I) measurable disease: complete response (CR) = disappearance of all known disease, determined by 2 observations not less than 4 weeks apart; partial r. (PR) = 50 % or more decrease in total tumour size of the lesions which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart (there can be no appearance of new lesions or progression of any lesion); no change (NC) = 50 % decrease in total tumour size cannot be established nor has a 25 % increase in the size of one or more measurable lesions been demonstrated; progressive disease (PD) = 25 % or more increase in the size of one or more measurable lesions, or the appearance of new lesions; (II) unmeasurable disease: complete r. (CR) = complete disappearance of all known disease for at least 4 weeks; partial r. (PR) = estimated decrease in tumour size of 50 % or more for at least 4 weeks; no change (NC) = no significant change for at least 4 weeks; this includes stable disease, estimated decrease of less than 50 %, and lesions with estimated increase of less than 25 %; progressive disease (PD) = appearance of any new lesion not previously identified or estimated increase of 25 % or more in existent lesions; (III) response criteria for bone

metastases: complete r. (CR) = complete disappearance of all lesions on X-ray or scan for at least 4 weeks; partial r. (PR) = partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions or observation of any progression for at least 4 weeks; no change (NC) = because of the slow response of bone lesions the designation "no change" should not be applied until at least 8 weeks have passed from the start of therapy; progressive disease (PD) = increase in size of existent lesions or appearance of new lesions; duration: CR lasts from the date of its first record to the date of first observation of progression; overall r. lasts from the first day of treatment to the date of first observation of progression; see also PERFORMANCE STATUS.

restricted marketing authorization see CONDITIONAL APPROVAL, LEGAL STATUS, MARKETING AUTHORISATION POST-MARKETING SURVEILLANCE.

results (of a clinical trial) Results should be reported to the competent authorities within one year of the end of the clinical trial.

retain samples In many countries (e.g. in Germany) national regulations request that samples of drugs used in clinical trials are kept for control purposes beyond termination of the trial; see also REFERENCE SAMPLE, RETENTION SAMPLE.

retention sample syn. Retain sample, reserve sample; (EU Guide to GMP) "A sample of a packaged unit from a batch of finished product for each packaging run/trial period"; it is stored for identification purposes; for example, presentation, packaging, labelling, leaflet, batch number, expiry date should the need arise; samples of each API BATCH should be retained for 1 year after the EXPIRY DATE of the batch assigned by the manufacturer or for 3 years after distribution of the batch, whichever is longer; the quantity must be sufficient to conduct two full analyses; see also REFERENCE SAMPLE.

retest date syn. retest period; for active pharmaceutical ingredients a retest period is to be defined, whereas the term SHELF-LIVE is commonly used for the finished pharmaceutical product; in clinical trials with new substances data on long term stability are frequently not available; in these cases a provisional expiry date is given that may be prolonged as soon as new stability data become available; see also EXPIRY DATE, STABILITY TEST.

retrospective study Opposite: prospective study; see PROSPECTIVE STUDY.

retroviruses DNA viruses that can integrate into host-DNA; they can be pathogenic (e.g. HIV) or oncogenic (leukaemia viruses) but have also a potential for GENE THERAPY; see GENOME.

return EC (IV): "sending back to the MANUFACTURER or distributor of a MEDICINAL PRODUCT which may or may not present a QUALITY DEFECT".

revocation of marketing authorization see WITHDRAWAL.

ribozyme Ribonucleic enzymes; class of new therapeutics planned for the treatment of viral infections, autoimmune disease, endocrine disease and cancers; like ANTISENSE OLIGONUCLEOTIDES they suppress gene expression by binding to mRNA templates, thus suppressing mRNA translation and therefore the production of disease-causing proteins; see, GENE THERAPY, RIBOZYME.

risk "combination of probability of harm and severity of that harm" (Source: ISO Guide 51; ICH Q9step4, QRM); Absolute r. = r. of developing the condition (disease) or outcome/response (e.g. cure, ADVERSE EFFECT) if the SUBJECT participates in/takes the putative cause; in the control group this is the r. of developing the condition/outcome if the subject did not participate/take the cause; relative r. = r. of developing the condition if the subject participates, divided by the r. of developing that condition if the subject does not participate (or if the risk factor is not used; usually estimated in COHORT studies; a relative risk <1.0 provides evidence for a positive association, i.e. incidence rate of exposed persons is lower than for non-exposed); attributable r. = r. of developing the condition if the risk factor is present minus the r. of developing the condition if the risk factor is absent divided by the r. of developing the condition if the risk factor is present; see also ADVERSE REACTION, ASSOCIATION TRIAL, EMPIRIC RECURRENCE RISK, ENVIRONMENTAL RISK ASSESSMENT, MIGRATION STUDY, RISK MANAGEMENT.

risk-benefit analysis see DECISION ANALYSIS, PERIODIC BENEFIT-RISK EVALUATION REPORT.

Risk Evaluation and Mitigation Strategies (REMS) Basically a 'benefit-risk' document approved by the FDA. The FDA (Amendments Act of 2007) requires REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks; see DIRECT HEALTH CARE PROFESSIONAL COMMUNICATION; DEAR DOCTOR LETTER, PERIODIC SAFETY UPDATE REPORT (PSUR).

risk factor Independent VARIABLE in ASSOCIATION STUDIES; the r.f. often precedes the outcome (dependent variable).

risk management plan (RMP) A "detailed description of the RISK MANAGEMENT SYSTEM" (Dir 2010/84); it includes also a summary of the safety profile, important identified risks (e.g., populations at risk) and important missing information (e.g., populations where the product might be used) concerning a medicinal product; it consists of a non-clinical part and a clinical part, and it includes a description of (planned) risk minimisation activities, if applicable; a RMP may need to be submitted during the pre-authorisation phase as well as

after MA; in contrast to the PSUR which covers just the time since the last PSUR, the RMP is cumulative; see also EUDRA VIGILANCE, RISK MINIMISATION ACTION PLAN.

Risk Management Plan Annex 1 (EU-RMAP Annex 1) is the electronic interface for EudraVigilance, to allow for the monitoring of identified and potential risks and important missing information in relation to suspected adverse reactions reported to EudraVigilance for centrally authorised medicinal products; see also CENTRALIZED PROCEDURE.

risk management system (RMS) (Dir. 2010/84/EC, EMA, Vol.9A, Part I, 3.2): "a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions"; examples of such activities are: (i) risk detection (e.g., patient REGISTRY), (ii) risk assessment (hazard analysis, e.g., SIGNAL DETECTION), (iii) risk control (e.g., pharmacovigilance systems, PASS), (iii) risk review (e.g., PERIODIC SAFETY UPDATE REPORT, PERIODIC BENEFIT RISK EVALUATION REPORT), (iv) risk communication (e.g.: "Dear Doctor Letter", DIRECT HEALTH CARE PROFESSIONAL COMMUNICATION); it may include also recommended measures for ensuring the safe use (r. minimisation); (v) risk minimisation (e.g., by restrictions/changes in the SUMMARY OF PRODUCT CHARACTERISTICS); see also COUNTERFEIT MEDICINE, EUROPEAN DATABASE OF SUSPECTED ADVERSE REACTION REPORTS.

Risk Minimisation Action Plan (Risk-MAP) FDA: A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting; see also LEGAL STATUS, PHARMACOVIGILANCE, POST-AUTHORISATION SAFETY STUDY, REGISTRY, RESTRICTED MARKETING AUTHORISATION, RISK MANAGEMENT PLAN, SURVEILLANCE.

Ritchie index Index used in rheumatology, measuring tenderness and inflammation of joints where 0 = not tender, 1 = tender, 2 = tender and winces, 3 = tender, winces and withdraws; see also ORDINAL SCALE.

RNA interference (RNAi) Process by which small double-stranded RNA molecules (dsRNA) induce homology-dependent inhibition of gene expression ("co-suppression")/(post-transcriptional down regulation); two distinct pathways are known: transcriptional gene silencing (TGS) and post-transcriptional gene silencing (PTGS) into short interfering RNA (siRNA); siRNAs are short-lived and interfere with effector proteins; see also MICRO RNA, NUCLEOTIDES.

Rohrer index Index used to describe the relationship between weight (body mass M) and height (L) in order to allow categorisation of subjects according to obesity; R = M/L3; see BODY-MASS-INDEX (QUETELET'S INDEX), LORENTZ FORMULA, WEIGHT.

Rote Liste see NATIONAL DRUG LIST.

route of administration oral: absorption is most readily with non-ionized lipid-soluble drugs (e.g. ethanol), a FIRST-PASS EFFECT is observed with some drugs; food can prolong absorption; some drugs (e.g. acetylsalicylic acid, barbiturates, ethanol) decrease gastric emptying; dermal: lipid-soluble drugs are readily absorbed through the skin, reduced blood flow reduces also absorption; inhalation: water soluble gases are almost immediately absorbed; particles less then 1 mcm in diameter can easily penetrate the lower airways; intramuscular: high variability from patient to patient; intravenous: most rapid and most reliable route of administration; nasal: most drugs with a molecular weight <300 DA penetrate the nasal epithelium with ease; benefits for nasal delivery of systemically acting drugs can include improved patient compliance, rapid onset of action, avoidance of first pass metabolism, improved bioavailability and increased cost-effectiveness; rectal: erratic absorption is frequent; drugs do not pass through liver before entering the general circulation; see ABSORPTION, ADME.

routine monitoring visit see PERIODIC SITE VISIT.

rule 80/125 FDA bioequivalence guidance for log-transformed data; the 80/125 rule concludes BIOEQUIVALENCE if $\mu T/\mu R$ falls within (80 %, 125 %) with 90 % assurance (μR, μT – average of the pharmacokinetic response of interest, say AUC or Cmax of test and reference substance); this rule is accepted by all major health authorities including the European CPMP and the Canadian Health Protection Branch; see also BIOLOGICAL EQUIVALENT, DRUG COMPARABILITY STUDY, PHARMACEUTICAL EQUIVALENT, THERAPEUTIC EQUIVALENT.

rule of three The upper 95 % CONFIDENCE INTERVAL (CI) of the estimate of the rate of an event can be easily calculated from the so called rule of three, whereby the value of 3 is an approximation for 2.996 (natural logarithm of 0.05×-1): upper 95 % confidence interval CI = 3/number observed; a study with a NSAID that follows e.g. 300 patients and that shows no development of gastric ulcer would have a best estimate of a rate of zero, with an upper 95 % CI of 1 in 100; the arbitrary 'rule of three' is based on the experience that for any given adverse effect approximately threefold the number of patients need to be treated and observed for the side effect to become manifest and reliably linked with the drug, assuming a background incidence of zero of the effect being observed or a clear, unambiguous causal association with the drug; see also ADVERSE EVENT.

run-in phase Phase prior to administration of a new drug or treatment; often a pretreatment phase (before any medication) in CLINICAL TRIALS; is useful e.g. for assessing BASELINE VARIABLES, elimination of non-compliers, reducing VARIABILITY and WITHDRAWALS, familiarisation with techniques of measurements to avoid SEQUENCE EFFECTS a.s.o.; often patients shall also have been off previous drugs before a new treatment starts, esp. if the previous drug has a prolonged duration of action; usually 2–4 weeks will be acceptable (WASH-OUT PERIOD); on the other hand, run-in phases result in selection of subjects and the trial population may therefore no longer be representative of all patients; furthermore, it may not be possible to leave patients untreated or to give placebo for a longer period of time by ethical reasons; see also REGRESSION PARADOX.

S

safety alert Voluntary communication by a manufacturer, distributor or health authority to inform health professionals of an unreasonable risk to the public health by a commercialised medicinal product or device intended for human use; this may be followed by a TYPE II VARIATION PROCEDURE; see also URGENT SAFETY RESTRICTION.

safety analysis Comprehensive summary of ADVERSE EFFECTS (AE); includes close examination of patients who either died during the study or left the study because of AEs; a common form for presentation of data are TRANSITION SCALES/SHIFT TABLES; in addition, tabulating the number of events in each category which may be a body system (e.g., cardiovascular), an organ (e.g., liver) or class (e.g., allergic) sometimes called System-Organ Class Frequency and/or analysis of time trends, may be a useful approach; see also DATA AND SAFETY REVIEW BOARD, NUMBER NEEDED TO HARM, WHO-ADVERSE REACTION TERMINOLOGY.

safety communication Information on medicinal products to patients and healthcare professionals, in particular on new, important aspects; communication tools and channels are variable and not restricted to (news)letters; important safety announcements should always be coordinated with the health authorities; see CONSUMER REPORTS, "DEAR HEALTHCARE PROFESSIONAL" LETTER, DIRECT HEALTH CARE PROFESSIONAL COMMUNICATION, PATIENT INFORMATION/PACKAGE LEAFLET, SUMMARY OF PRODUCT CHARACTERISTICS.

safety officer EMA requests that each company has a permanent person in a member state responsible for PHARMACOVIGILANCE; see QUALIFIED PERSON.

safety report see INDIVIDUAL CASE SAFETY REPORT.

safety specification Summary of important identified risks of a medicinal product as included in the RISK MANAGEMENT PLAN.

G. Nahler, *Dictionary of Pharmaceutical Medicine*,
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safety tests Toxico-pharmacological test, as well as tests on sterility, bacterial endotoxin, pyrogenicity, and local tolerance.

safety update report see DEVELOPMENT SAFETY UPDATE REPORT, PERIODIC SAFETY UPDATE REPORT.

safety variation application see TYPE II VARIATION, URGENT SAFETY RESTRICTION.

sales reps Sales representatives of pharmaceutical companies; in some countries (e.g. Austria, France) professional training of s.r. is regulated, requiring formal certificates of successful training; in France it is also requested that badges be worn with the name of the s.r. and the company.

sample size estimation The number of subjects necessary in a study (Number Needed to Treat) depends on the VARIANCE, the magnitude of difference to be detected (DELTA VALUE), and the desired POWER; in order to comply with EC guidelines "the potential for reaching sound conclusions with the smallest possible exposure of subjects" has to be considered in trial protocols; for s.s.e. the "hypothesis testing approach" is most common, which determines whether some appropriate comparative measure (such as the difference between MEANS or a relative risk) is significantly different from its null value (e.g. a mean difference of zero or a relative risk of one); a "confidence interval approach" however would concentrate on an estimation of the comparative measure together with its CONFIDENCE INTERVALS; see also EFFECT SIZE.

sampling error ERROR introduced by the chance difference between an estimate obtained from a sample and the true value in the population from which the sample was drawn; see INTENT-TO-TREAT LIST.

sanctions Regulatory actions that apply to medicinal products, devices, their manufacturers and distributors, when they are discovered to be in violation of FDA or other regulatory requirements: detention, seizure, FDA initiated or voluntary recall, suspension/WITHDRAWAL of marketing authorization, regulatory letter, citation, injunction, and prosecution; between 2007 and 2012 life science companies have paid an estimated sum of 15 billion US $ in fines and compliance related settlements by governments; see also BLACK LIST.

scales Instruments for measuring "hard-to-quantify" variables, i.e. non-dimensional, ORDINAL DATA; a number of different types exist, e.g. Alzheimer's Disease Assessment Scale – ADAS; LIKERT SCALE, Mini-Mental State Examination – MMSE, VISUAL ANALOGUE S., ladder s., pictorial s., "faces" s., delighted-terrible s., a.s.o.; scales are commonly used for assessing e.g. the PERFORMANCE STATUS, HEALTH PROFILE, QUALITY OF LIFE, WELL-BEING, a.s.o.; scales (and results) differ whether they are intended to be used by a

trained interviewer, by a physician, by family members or as self-report/self-administered s.; see also HAWTHORNE EFFECT, INDEX, ORDINAL SCALE, QUALITY OF LIFE SCALE, SCORE, STAGING, WELL-BEING SCALE.

school medicine see CONVENTIONAL MEDICINE.

science impact index (SII) Reflects scientific merit of an author; it represents the different researchers (or research groups) worldwide who annually quote a paper of a specific author (as revealed by the Science Citation Index).

scientific advice see DEVELOPMENT SAFETY UPDATE REPORT.

score Basic requirements for a score are: high SENSITIVITY, RELIABILITY, good repeatability (both inter- and intra-observer), VALIDITY and good correlation with other tests; see also COMPOSITE VARIABLE, GENIE SCORE, GLOBAL ASSESSMENT VARIABLE, INDEX, SCALES, STAGING, VARIABLE.

search engines Internet-based search engines for medical literature include Google, Google scholar, Yahoo search engine, etc., see also LITERATURE SEARCH.

secondary attack rate The number of exposed people in whom the disease develops within the range of the INCUBATION PERIOD compared with the number of individuals exposed to the primary patient; s.a.r. is a PROPORTION, not a RATE; s.a.r. are used to determine whether a disease of unknown aetiology is communicable and thus may indicate a transmissible aetiology; see ATTACK RATE.

secrecy agreement see CONFIDENTIAL DISCLOSURE AGREEMENT.

seeding activity see MARKETING STUDY.

selected list scheme (SLS) List of pharmaceuticals which are exempted from REIMBURSEMENT by national health services.

selection criteria see ELIGIBILITY C.

self-inspection Part of a quality assurance system in order to monitor the implementation and respect of e.g. GMP or GCP and to propose any necessary corrective measures; see also INSPECTION.

self-medication Opp. prescription-only medication (POM); use of non-prescription medicines (OTC) by people on their own initiative; in most countries OTCs are not subject of price control (in Europe all countries except Austria and Hungary); in 1994, average European OTC sales in percent of POM sales were approx. 25 %, with values up to 45 % (Poland) or as low as 10 % (Austria, Hungary); see also OVER-THE-COUNTER.

self-regulatory industry control see CODES OF PRACTICE.

sensitivity Number of positive cases in patients with the DISEASE, i.e. number of true positive results of a test divided by the total number of true positive plus false negative test results; see also PREDICTIVE VALUE, SPECIFICITY.

sentinel sites Active surveillance for adverse reactions of a drug by reviewing medical records and/or interviewing patients or physicians on a sample of sites (hospitals, nursing homes, haemodialysis centres etc.); see also INTENSIVE MONITORING, PHARMACOVIGILANCE, PRESCRIPTION EVENT MONITORING, SOLICITED REPORT.

serendipity Unexpected pharmacological activity discovered during drug development (e.g., clonidin was intended for common cold but is a central antihypertensive; sildenafil was reprofiled from angina and hypertension to erectile dysfunction; see also DRUG REPOSITIONING.

serious adverse reaction are to be reported to the authority within 15 days at the latest; ~320,000 suspected serious adverse reaction reports are managed annually (2008) at level of the European Community; during 2010, the FDA received 409,608 reports describing a serious outcome that is not currently listed and 28,952 reports from non-manufacturers such as patients, physicians, family members or lawyers; see ADVERSE REACTION.

sequence effect Types are: carry-over e.: (biological) effect continues after the treatment is withdrawn and after complete disappearance of the DRUG from the body; order e.: if diagnoses, observations, assessments, techniques a.s.o. become (gradually) more precise as result of a training or learning process e.g. of the observer; (esp. important in surgical trials); time-treatment interaction: if different results occur in one treatment period compared with another one; e.g. PLACEBO may be more effective when given first to lower blood pressure or when given last to relieve a painful condition that is improving with time; any s.e. will compromise particularly cross-over DESIGNS; also important with respect to RUN-IN PHASES of trials.

sequential design In this DESIGN the conduct of the trial depends at any stage on the results so far obtained; in contrast to most other designs patients are usually entered simultaneously in pairs, one patient receiving A and the other B (comparison between subjects), but comparison within subjects may also be possible; response is assessed in sequential order, therefore allowing termination as soon as the predefined boundaries of significance (A better, equal, worse than B) are reached; special types: group sequential d., full sequential d.; such designs can be useful e.g. for the evaluation of cough suppressants, analgesics, preferences of taste a.s.o., whenever the response is obvious soon after treatment and when BIAS can be ruled out.

shelf life see EXPIRATION DATE, RETEST DATE, STABILITY TEST.

shift table syn. Transition matrix; table showing the number of patients who are low, normal, or high at baseline and at selected time intervals; shift tables are of particular importance in reports; see also TRANSITION MATRIX.

short interfering RNA (siRNA) see RNA INTERFERENCE.

side effect The former definition "a response to a (registered) drug which occurs when used as indicated in the current labelling" (EU Dir 2001/20) has been changed by Dir 2010/84 and includes now adverse reactions that occur when the drug is not taken as directed (i.e. "outside the terms of the marketing authorisation"); this would include, e.g. overdose, MEDICATION ERRORS, OFF-LABEL use, occupational exposure, etc.; the PACKAGE INSERTS continue to include only those s.e. that "may occur under normal use"; the term s.e. is used in various ways (e.g. WHO: "Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug"), usually to describe negative or unfavourable effects but also positive effects; see ADVERSE DRUG REACTIONS, CONSUMER REPORT, DATA AND SAFETY REVIEW BOARD, DRUG INJURY, INDIVIDUAL CASE SAFETY REPORT, UNDESIRABLE EFFECT.

signal def. (WHO): reported information on a possible causal relationship between an ADVERSE EVENT and a DRUG, the relationship being unknown or incompletely documented previously; usually more than a single REPORT (also called Drug-Event Combination, DEC or Drug-Event Association, DEA) is required to generate a signal, depending upon the seriousness of the event and the quality of the information; examples of signals: new, previously unrecognized adverse events; increase in frequency of known events; increase in severity or specificity of known events; drug interactions, food or dietary supplements, lack of efficacy, concomitant diseases, etc.; product use issues (e.g. off label administrations, misuse, medication errors); risk in special populations; see also DISPROPORTIONALITY ASSESSMENTS, PHARMACOVIGILANCE, RULE-OF-THREE.

signal detection Part of routine safety monitoring activities; it includes the interpretation of safety data from all sources, preclinical, clinical, post approval and externally; it is directed towards the identification and evaluation of safety risks from reported adverse reactions & potential risk factors for this ADVERSE REACTION; a traditional method would be the manual review of ICSR lists; however, higher order associations (e.g., drug-drug interactions, drug-food-interactions, multiple risk factors for developing an AE, etc.) are particularly difficult to be captured by the human mind by traditional methods; common data mining algorithms are basing on DISPROPORTIONALITY ASSESSMENTS or on empirical Bayesian methods such as the multi-item gamma Poisson Shrinker

used by the FDA or the Information Component used by the WHO Monitoring Centre in Uppsala; differential reporting is not necessarily indicative of differential occurrence; see also BAYESIAN ADVERSE REACTION DIAGNOSTIC INSTRUMENT, BIAS, DATA MINING, DUPLICATE REPORT, PHARMACOVIGILANCE, PROTOPATHIC BIAS, SIMPSON'S PARADOX.

signal fragmentation see DATA MINING.

signal transduction The molecular pathways mechanism through which a cell senses changes in its external environment and changes its gene expression patterns in response.

signature sheet see AUTHORISATION FORM.

significance level Probability of a type I (ALPHA) ERROR, statistical significance should always be seen in the light of clinical relevance; see also DELTA VALUE.

significant adverse event: Event leading to discontinuation or dose modification; such event is considered to be a (immediately) reportable (to the sponsor) ADVERSE EVENT. Significant AEs have to be reported separately in the INTEGRATED REPORT.

significant change see STABILITY TEST.

significant overdose Cases in which the dose taken is greatly in excess (>5 times) of the recommended maximum dose in the summary of products characteristics (SPC), whether intentionally or unintentionally (EC); see also ADVERSE REACTION.

signs Visible, palpable, audible or objectively measurable forms of manifestation of a DISEASE, e.g. enlarged lymph nodes, enhanced erythrocyte sedimentation rate a.s.o.; see also SIMPSON'S PARADOX, SYMPTOMS.

sign test Simple, nonparametric statistical test for specific sets of data (characteristic quality is present or not).

Simpson's paradox syn. Yule-Simpson effect; it means that an association between two variables is reversed upon observing a third variable such as age or severity of disease that act as CONFOUNDERS; the Simpson's paradox may led to false conclusions in efficacy studies and pharmacovigilance; it occurs in medical-science and social-science statistics and disappears when causal relations are derived more systematically; see also CONFOUNDER, DATA MINING, PHARMACOVIGILANCE.

single-blind see BLINDING.

single case experiment Also N of 1 study, case-crossover study, intensive research DESIGN; investigation with a sample size n = 1, whereby a single SUBJECT receives effective treatment and PLACEBO (or a control therapy)

sequentially and at random (usually several of such paired treatment periods) to determine whether a treatment is beneficial (causing side effects) or not; patient and clinician should be kept blind; only applicable if the clinical condition is fundamentally stable and if improvement and deterioration occur rapidly with respect to treatment changes; see also DESIGN.

single coded see CODE.

single-dose toxicity syn. acute toxicity; see TOXICITY.

single nucleotide polymorphism (SNP, pronounced "snips") variation at just a single base of a four-bases (syn. nucleotides) long codon (point mutation) resulting in at least two different alleles for a gene; it is assumed that SNPs predispose individuals to develop certain diseases but also to respond or not to certain drugs; as example, approx. 20 % of the Western European population are homozygous for one of the mutations the Methylene-Tetra-Hydro-Folate-Reductase (MTHFR) gene which is supposed to result in reduced MTHFR activity and in higher baseline plasma homocysteine levels; see also ALLELE, GENETIC POLYMORPHISM, GENOM, PHARMACOGENETICS, POLYMERASE CHAIN REACTION, POLYMORPHISM.

single-site trial syn. single centre study; trial conducted at only one centre; advantages versus a MULTICENTRE TRIAL: easier to control, lower costs, EFFECT size may be larger due to more pronounced homogeneity, decision making is more efficient.

site audit see AUDIT.

site management organisation (SMO) Trial management organisation integrating clinical project management and study conduct activities; see CLINICAL RESEARCH ORGANISATION.

site master file (SMF) Document that describes the GMP-related activities of the manufacturer; see GOOD MANUFACTURING PRACTICE.

site visit log see MONITOR'S VISIT LOG LIST.

skewness Asymmetry of the DISTRIBUTION of DATA; a distribution is skewed to the right, when the MEAN exceeds the MEDIAN and the right tail is therefore longer than the left (typical for variables with a fixed lower but without upper bound, e.g. number of episodes); opp. NORMAL distribution; see also CEILING EFFECT, FLOOR EFFECT.

slow metaboliser Subject with a variant gene of a specific enzyme (not totally inactivating the activities) because of alterations of the DNA; see ETHNIC DIFFERENCES, GENETIC POLYMORPHISM, METABOLISM, PHARMACOGENETICS, POOR METABOLISER.

slow release formulation (SR) opposite: immediate release form; see CONTROLLED RELEASE FORM, FORMULATION.

small and medium sized enterprises (SME) Enterprises with <250 employees and an annual turnover of ≤50 million Euro and/or an annual balance sheet of ≤43 million Euro (EC); such enterprises benefit of reduced fees payable to EMA (Annex to Commission Recommendation 2003/361/EC); see also EUROPEAN MEDICINES AGENCY, MICRO-ENTERPRISE.

SNOMED Systematized Nomenclature of Medicine, see CODE.

solicited report Reports derived from organized data-collection schemes; see CLINICAL TRIAL, INTENSIVE MONITORING, NAMED PATIENT USE, PHARMACOVIGILANCE, POST-APPROVAL SAFETY STUDY, PRESCRIPTION EVENT MONITORING, REGISTRY, SENTINEL SITES.

source data syn. original medical record, source document; patient files, original recordings from automated instruments, tracings (ECG, EEG), X-ray films, laboratory notes, patient diaries, a.s.o., in short: place where information is first recorded; s.d. can also be the original electronic file (preferably recorded on a durable electronic medium); source data is the responsibility of the investigator who must maintain full (also archival) control of them; s.d. must be contemporaneous, original, attributable, legible and accurate/complete; see also DATA QUALITY, ELECTRONIC DATA, RAW DATA.

source data verification (SDV) Also s.d. validation; procedures to ensure that data contained in the CASE RECORD FORM (CRF) and later in the FINAL REPORT match original observations; these procedures (AUDIT, INSPECTION, QUALITY CONTROL) may apply to RAW DATA, hard copies, electronic CRFs, computer printouts, statistical analyses, tables etc.; s.d.v. should be carried out on KEY DATA items (patient identification, CONSENT form, ELIGIBILITY CRITERIA, drug administration, EFFICACY, safety) to an extent of 100 % and on other items of data to an extent of about 20 %; should however errors appear at a frequency of greater than 15 % intensive s.d.v. will generally be required; EC: "statistically controlled sampling may be an acceptable method of data verification"; ICH guideline on GCP requests "direct access to the subject's original medical records"; the interview-technique or back-to-back method across the table is no longer acceptable from 17. January 1997 onwards; see also DATA QUALITY.

source document see CASE RECORD FORM, DATA CAPTURE DOCUMENT, SOURCE DATA.

specification see PRODUCT SPECIFICATION.

specificity Number of negative cases in patients free of DISEASE, i.e. true negative results of a test divided by the total number of true negative plus false positive test results; see also PREDICTIVE VALUE, SENSITIVITY.

sponsor syn. promoter; organization or individual who takes responsibility for the initiation, management and/or financing of a trial; responsibilities (FDA): "… for selecting qualified INVESTIGATORS, providing them with the information they need to conduct an investigation properly, ensuring that the investigation is conducted in accordance with the general INVESTIGATIONAL PLAN and PROTOCOLS contained in the IND (INVESTIGATIONAL NEW DRUG), maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new ADVERSE EXPERIENCES or risks…"; (EC): "to establish detailed STANDARD OPERATING PROCEDURES, to appoint and train MONITORS, to prepare REPORTS irrespectively whether the trial is completed or not, to provide adequate compensation for subjects in case of injury or death and indemnity for the investigator, to inform investigator and relevant authorities, to maintain records of products supplied (DRUG ACCOUNTABILITY), to conduct an internal AUDIT, to ensure identification of all data and accuracy when transforming data".

sponsor-investigator Individual who both initiates and actually conducts, alone or with others, a clinical investigation (investigator initiated trial, sponsor-investigator study), i.e., under whose immediate direction the test article is administered or dispensed to, or used involving a subject; the term includes no other person than an individual, e.g. corporation or agency; in US this individual can get a personal IND (INVESTIGATIONAL NEW DRUG); see also NON-COMMERCIAL CLINICAL TRIAL, PHYSICIAN INVESTIGATOR.

spontaneous adverse drug reaction report ICH: "An unsolicited communication to a company, regulatory authority or other organisation that describes an adverse medical reaction in a patient given one or more MEDICINAL PRODUCTS and which does not derive from a study or any organised data collection scheme"; see also INDIVIDUAL CASE SAFETY REPORT, PHARMACOVIGILANCE, PRESCRIPTION EVENT MONITORING, SOLICITED REPORT.

spontaneous notification see SPONTANEOUS ADVERSE DRUG REACTION REPORT.

spontaneous reporting scheme syn. spontaneous report system, e.g. the YELLOW CARD PROGRAMME in UK, Sweden, Norway or the BLUE CARD SYSTEM in Australia; either a voluntary or mandatory reporting of usually serious ADVERSE EVENTS (AE), in some countries directly to manufacturers (majority of all such reports e.g. in US, Japan, Germany), whereas in other countries they are initially received by a health authority; advantages: clinical immediacy, low cost, application to all drugs in use at all time, generates the initial alert; disadvantages: lack of CONTROL data, inability to quantify AEs in relation to drug use (under-reporting), BIAS introduced by inconsistency in level

of under-reporting (it is estimated that only about one case out of 10 to one out of 1.000 is actually reported, severe AEs are much more likely to be reported than minor reactions); the amount of information obtained is also very limited, e.g. there is no recording of the ethnic origin in the CIOMS-FORM or YELLOW CARD; beside spontaneous reports of AEs, some countries request notification of all events, including reports e.g. in literature; see also DRUG SAFETY MONITORING, DRUG INJURY, PRESCRIPTION-EVENT MONITORING.

spontaneous report system see SPONTANEOUS REPORTING SCHEME.

spurious data see FRAUD.

square-root rule When costs of treatment vary, UNEQUAL RANDOMIZATION may be employed: when it costs r times as much to study a subject on treatment A than on B then one should allocate $=+r$ times as many patients to B than to A.

s-2 report Report to be submitted by the sponsor to the FDA, if serious adverse effects are observed in preclinical safety studies being conducted after the initial investigational new drug (IND) submission; notification must be made as soon as possible but not later than 10 days after the sponsor is aware of the information; see also ADVERSE REACTION.

stability test Data on the long term stability are required when submitting a pharmaceutical product for marketing approval; such test has to be conducted usually at 25 ± 2 °C, at 60 ± 5 % relative humidity (RH), with min. 3 batches, monthly for the first 3 months, at 3-m intervals thereafter and for a minimum of 12 months; longer s.t. must be performed at least annually; stability studies should be performed on each individual strength, dosage form and container type (e.g., semi-permeable/impermeable to moisture) and size proposed for marketing; a provisional extrapolation of stability data may be acceptable as long as no "significant change" occurred, i.e. a 5 % or more change from its initial content of API(s), or failure to meet the acceptance criteria (e.g., in terms of potency, degradation products, appearance, etc.); stability can be influenced, among other factors, by the crystalline form of the substance; see also CLIMATIC ZONES, IMPURITY, RETEST DATE, SHELF-LIVE, STRESS TESTING.

Stability test	Storage condition	Minimum period covered by data at submission (months)
Long term	25 ± 2 °C/60 % RH ± 5 % RH, or[a]	12
	30 ± 2 °C/65 % RH ± 5 % RH; or[b]	
	30 ± 2 °C/75 % RH ± 5 % RH	
	(5 ± 3 °C)[c]; (−20 °C ± 5 °C)[d]	

Stability test	Storage condition	Minimum period covered by data at submission (months)
Intermediate	30 ± 2 °C/65 % RH ± 5 % RH; (25 ± 2 °C/60 % RH ± 5 % RH)[c]	6 (designed to moderately increase the rate of degradation for a product intended to be stored long term at 25 °C)
Accelerated	40 ± 2 °C/75 % RH ± 5 % RH; (25 ± 2 °C/60 % RH ± 5 % RH)[C], OR (30 ± 2 °C/65 % RH ± 5 % RH)[a]; or (30 ± 2 °C/75 % RH ± 5 % RH)	6
Stress	Temperatures above that for accelerated testing (in 10 °C increments, e.g., 50 °C, 60 °C, 75 % RH or greater, increments of 5 %)	–

[a]Up to the applicant to decide (risk-based)
[b]Climatic zone IV
[c]Drug substances intended for storage in a refrigerator
[d]Drug substances intended for storage in a freezer

stabilizer see EXCIPIENTS.

staff log see AUTHORISATION FORM.

staggered dosing approach; see PHASE I.

staging Assessment systems used to classify patients with respect to severity of disease, treatment strategies, and prognostic categories; see CLASSIFICATION OF RECURRENCE, DISEASE FREE INTERVALL, SCALES, SCORE, TNM-STAGING, TUMOR STAGING.

stakeholder Any individual, group or organization; the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

standard deviation (SD) Square root of the sum of squares of deviation divided by one less than the number of squares in the sum; when DATA are normally (symmetrically) distributed (observations are equally likely to be above or below the MEAN and more likely to be near the mean than far away, Gaussian curve), 68.2 % of them will fall within ± one, 95.5 % within two and 99.7 % within three standard deviations; see also DISTRIBUTION, OUTLIERS, OUT-OF-RANGE VALUES.

standard error Measure of the inherent VARIABILITY of the estimate; the standard error of the MEAN (SEM) = STANDARD DEVIATION of the raw data divided by square root of the number of observations.

standard gamble Instrument for UTILITY or QUALITY OF LIFE measurements; patients are asked to choose between their own HEALTH status and a gamble in which they may die immediately or achieve full health for the remainder of their lives; numeric values are determined by the choices patients make as the probabilities of immediate death or full health are varied.

standardized assessment of causality (SAC) Algorithm for the objective determination of a putative relationship between an ADVERSE EFFECT and a given DRUG; it consists of a series of questions which can be either answered by "yes", "no" or "unknown" or for which plus or minus point scores are given; at the end a CAUSALITY assessment is made by calculating the number of points; depending on the point score, the strength of a causal relationship is then considered such as "definite, probable, possible or unlikely"; results of SAC show most often only very little inter-observer variability in contrast to causality assessments after WHO or Karch & Lasagna; examples of algorithms utilized are the Kramer a. (56 questions to answer), the Jones a. (6 questions), and the NARANJO a. (10 questions); inclusion of diagnostic criteria set by experts or the Bayesian approach may also be a suitable method; see ADVERSE DRUG REACTION, BAYESIAN ADVERSE REACTION DIAGNOSTIC INSTRUMENT (BARDI), CAUSALITY, DRUG INTERACTION PROBABILITY SCALE.

standardized decision aids (SDA) Methods that pose a series of predetermined questions which are usually answered by "yes", "no" or "unknown"; used also for CAUSALITY assessments of ADVERSE REACTIONS; see STANDARDIZED ASSESSMENT OF CAUSALITY.

standardized response mean (SRM) Calculated by dividing the mean change by the standard deviation of the change; see ANALYSIS, EFFECT SIZE.

standard operating procedures (SOP) Pre-established, systematic and written description of a specified activity such as the management, organisation, conduct, data collection, documentation and verification of a process, e.g. of manufacturing, quality control or of CLINICAL TRIALS; SOP should describe the step-by-step actions necessary to initiate and complete the task (including controls/validation) required in each job description; if necessary, they may be supplemented with written "working instructions" or manuals; SOP assure correctness, consistency and completeness in an operation and shorten training periods; EC guidelines request that sponsors "establish detailed SOPs to comply with GXP" (GOOD CLINICAL PRACTICE, GOOD LABORATORY PRACTICE, GOOD

MANUFACTURING PRACTICE, GOOD PHARMACOVIGILANCE PRACTICE a.s.o.) and that the monitor "works according a predetermined SOP".

Standards for the Reporting of Diagnostic accuracy studies (STARD) Standards to improve the accuracy and completeness of reporting of diagnostic studies (http://www.stard-statement.org); see also PUBLICATION GUIDELINES.

starting material EC: "any substance used in the production of a MEDICINAL PRODUCT, but excluding PACKAGING MATERIALS"; see also BATCH DOCUMENTATION, FINISHED PRODUCT.

start-up meeting see PRESTUDY MEETING.

statement of investigator EC: "administrative document maintained for each centre in the TRIAL MASTER FILE"; elements contain an identification (name, address) of the investigator, other research personnel assisting, site of centre, laboratory used, ethics committee responsible, title and protocol; the st. of I. must also contain a list of obligations, e.g. agreement to comply with the procedures defined in the protocol, to have read and understood the investigational drug brochure, to personally conduct, supervise and dedicate sufficient time to the study, to adequately inform subjects and obtain their consent, to report immediately to the sponsor all serious and unexpected adverse events, to maintain adequate and accurate records, to submit protocol, amendments, and material for informed consent to the ethics committee, that all personnel involved are informed about their obligations etc. this can be part of a contract; see also INVESTIGATOR.

statistical test see DATA; see also O'BRIAN PROCEDURE, PRIMARY ENDPOINT, WEILACHIN PROCEDURE.

steady state study Special DESIGN of a BIOAVAILABILITY study; requested when plasma concentration cannot be determined precisely, e.g. due to problems of sensitivity after single dose, intra-individual VARIABILITY in plasma concentrations, dose- or time-dependent PHARMACOKINETICS, extended release products a.s.o.

steering committee Trials which are likely to have a major impact on treatment habits are frequently "supervised" by a s.c.; this committee is scientifically responsible for the study plan, ev. decisions concerning stopping the trial prematurely and interpretation of study results; see also DATA AND SAFETY MONITORING BOARD.

stem cells (Immortalised) cells able to limitless self-renewal and to differentiate to all cell types in the body; they are derived from three main classes of cell lines, embryonic stem cells (ESC), adult stem cells (ASC) and induced pluripotent stem cells (iPSC); they may be used for in vitro toxicity testing as well as for therapeutic purposes; see STEM CELL THERAPY.

stem cell therapy (Immortalised) cells able to limitless self-renewal and to differentiate to all cell types in the body; they are derived from three main classes of cell lines, embryonic stem cells (ESC), adult stem cells (ASC) and induced pluripotent stem cells (iPSC); they can be transplanted into damaged tissue and effect repair; research concentrates e.g., on diseases of the central nervous system, namely Parkinson's disease, stroke, Huntington's chorea or diabetes type I; stem cell dysfunction may lead to tumour formation; host-induced immune response can also complicate the therapy see also ADVANCED THERAPY, CELLULAR REPROGRAMMING, PLASTICITY, REGENERATIVE MEDICINE.

stereoisomer Molecules differing only in their three-dimensional (geometric) structure (spatial orientation of the atoms or groups of atoms) but not in their chemical composition and formula; diastereoisomers are stereoisomers that are not enantiomers; see CHIRALITY, ENANTIOMER.

sterilisation Physical (e.g. by heat or steam) or chemical (e.g. by alcohol, ethylene oxide, formaldehyde, hydrogen peroxide) process to eliminate viable organisms.

sterility EC (IV): "absence of living organisms"; (conditions of the sterility test are given in the European Pharmacopoeia); ICH is likely to mandate that the maximum shelf life for sterile drugs after first opening or following reconstitution should be 28 days.

stochastic variable Variable involving random possibilities, chance or probability; see DATA.

stopping rules Study discontinuation criteria usually defined in the PROTOCOL; a trial should be stopped if e.g. substantial evidence (MAXIMUM ACCEPTABLE DIFFERENCE) of the superiority of one treatment (in terms of EFFICACY or safety) emerges, when the predetermined number of patients has been admitted and followed for a given length of time or when there is no hope of recruiting the required numbers for a given amount of time or money a.s.o.; see also INTERIM ANALYSIS.

stratification Method of ensuring that treatment groups will be balanced for prognostic factors known or strongly suspected to influence treatment outcome; after these factors (e.g. sex, age, severity or duration of DISEASE, concomitant diseases etc.) are decided upon, SUBJECTS with these VARIABLES are then distributed between the treatment groups or, more often, are randomized (stratified RANDOMIZATION) to treatment groups within each of these separate strata; this implicates separate RANDOMIZATION lists e.g. for males and females in case of s. according to sex; s. is of special importance in small trials with patient numbers considerably below 100–200 in each group since imbalances by mere chance become more likely; s. reduces BIAS, allows the

assessment of treatment EFFECTS separately for different subgroups, and enhances PRECISION of the study; excessive s. (overstratification) however is defeating and creates imbalances (rule of thumb: number of strata should not exceed the square root of the number of subjects); see also BALANCED STUDY, MINIMISATION.

strategic alliance Term used for describing a variety of interfunctional cooperative arrangements between individual companies, e.g. know-how exchange: such as cross-licensing, exchange of patent rights, mutual second-sourcing of raw material a.s.o.; collaborative R&D: companies whether competitors or not, share scientific, technological or other kind of information for mutual benefit; R&D joint ventures: creation of a separate corporate entity by at least two companies for pursuing a distinctive research program.

strength of medication; syn. potency; amount of ACTIVE PHARMACEUTICAL INGREDIENT per unit (e.g., "50 mg tablet") or concentration; 90 % of the declared potency is generally considered as the lowest acceptable level; see also DOSAGE REGIMEN, DRUG, MEDICINAL PRODUCT.

stress testing syn. accelerated testing; studies designed to increase the rate of chemical or physical degradation of a drug substance or DRUG PRODUCT by using exaggerated storage conditions to help identify the likely degradation products; as a rule of thumb the speed of a chemical reaction doubles with each increase of the temperature by 10 °C; the purpose is to determine kinetic parameters, and to predict the tentative expiration dating period/stability of a drug but also to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping); stress testing conditions usually include temperature, e.g. 50 °C, 60 °C (increments of 10 °C), to 75 °C), humidity, e.g. 75 % or greater (increments of 5 %), and exposure to various wavelengths of electromagnetic radiation (e.g. 190–780 nm, i.e. ultraviolet and visible ranges), preferable in open containers where applicable; usual stress testing conditions are 40 ± 2 °C, and 75 ± 5 % relative humidity, with analyses done every third month during the first year, every 6 month in the second, and then yearly; further stability studies may include: pH < or > 7.0, high oxygen atmosphere, presence of ADDITIVES as considered in final FORMULATION; DEGRADATION PRODUCTS should be identified and quantitatively assessed; stress t. may be carried out on a single batch of the API; see also STABILITY TEST.

strict liability; see INSURANCE.

STrengthening the Reporting of Observational studies in Epidemiology (STROBE) The statement is a reporting tool for OBSERVATIONAL STUDIES in EPIDEMIOLOGY; (http://www.strobe-statement.org/; http://www.annals.org/). See also PUBLICATION GUIDELINES.

study coordinator EC (III): "appropriately experienced person nominated by the INVESTIGATOR to assist administering the trial at the investigational site"; most often this will be a nurse or physician who takes care of and who coordinates the trial in terms of medical approach; she/he may also be the ultimate responsible person for the observation of the protocol, for observation of regulatory aspects, for the progress of the study, and finally for analysing and reporting the results.

study duration sum of recruitment duration + treatment duration (+ observation period, if applicable).

study identification code syn. study number; to each study a unique code should be assigned which is printed on all respective documents as e.g. case record forms, protocol, contracts a.s.o.; frequently a study has more than one code, e.g. an internal (company/sponsor) code, a "regulatory" code (e.g. EUDRACT number) and a project code of the CRO.

study list syn. masterplan, clinical program outline; table where all studies conducted with a particular drug (according to a pre-established PROJECT PLAN) are listed with study numbers for their identification, fields for a short information concerning the indication, trialists and centres resp., dose and forms used, projected patient numbers, PHASE, type and DESIGN of the trial, time lines, status a.s.o.; see also CLINICAL DEVELOPMENT PLAN.

study (site) coordinator On the investigational site, the study coordinator's activity ("study site coordinator", SSC) is often overlapping with the activities of a STUDY NURSE; see also CLINICAL TRIAL COORDINATOR.

study nurse syn. research nurse; nurse who is responsible for the on-site activity of a clinical trial; she is usually member of the staff of the trialist; she may enter the DATA into the CASE RECORD FORMS, organise investigations for patients, dates for visits, cooperate directly with the MONITOR of the company a.s.o.; see also CLINICAL RESEARCH ASSOCIATE, CLINICAL TRIAL COORDINATOR.

study plan see PROTOCOL.

study progress report syn. study status report; relevant regulatory authorities or ethics committees should be informed about the progress of a study (post-marketing safety study) every 6–12 months or as requested by the authorities/regulations; see ANNUAL PROGRESS REPORT, ANNUAL SAFETY UPDATE REPORT, see also REPORT.

study status report see STUDY PROGRESS REPORT.

study supplies All material needed for the proper conduct of a clinical trial, e.g. case record forms, drug supplies, protocol, informed consent forms a.s.o.

subacute toxicity see TOXICITY.

subgroup analysis Analysis performed when there is a particular interest in the results of a certain section of the trial participants (analysis according to sex, age groups, prognostic factors a.s.o.), usually in order to test or formulate new hypotheses; in pre-planned s.a. patients are randomized within strata (outlined in the protocol) to avoid unequal distribution; "post-hoc" s.a. however can cause severe BIAS by counterbalancing RANDOMIZATION, and by increasing the likelihood of a "significant" result by mere chance, which is proportional to the number of analysed subgroups (e.g. for five subgroups such as male/female, age ≤65/>65, concomitant disease yes/no, severity of disease below/above average, pretreated yes/no there is a 85 % probability to have a significant effect with $p<0.05$ in one subgroup); situations in which a treatment seems to be highly effective in only one subgroup, with a marginal or even unsignificant overall effect, should always be interpreted with caution; s.a. deal with fewer patients and will normally tend to produce less statistically significant results; see also INTERIM ANALYSIS, MULTIPLE COMPARISONS, STRATIFICATION.

subinvestigator see AUTHORISATION FORM, INVESTIGATOR.

subject Any individual participating as a volunteer in a clinical investigation, either as a recipient of the TEST ARTICLE or as a control; a subject may be either a healthy human or a patient; frequently, the term patient is preferred in clinical studies.

subject enrolment log syn. enrolment log list; to document chronological enrolment of subjects by trial number (ESSENTIAL DOCUMENT according to ICH).

subject-event monitoring see PHARMACOVIGILANCE, PRESCRIPTION-EVENT MONOTORING, SOLICITED REPORT.

subject identification code Unique identifier used in lieu of the subject's name (usually a alpha-numeric code) assigned by the investigator or sponsor to each trial subject to protect the subject's identity.

subject identification code list syn. patient log list, patient log book; code used in lieu of the subject's name; "to document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial" and "to permit identification of all subjects enrolled in the trial in case follow-up is required. The list should be kept in a confidential manner" (ICH E6, GCP); confidential list of names of all subjects allocated to trial numbers on enrolling in the trial, kept by the investigator, to permit identification of all subjects enrolled in the trial in case follow-up is required; the investigator must be able to identify the patient by its code; it is necessary therefore to have a (confidential) list exhibiting the codes as well as the complete identification of each patient (surname, given name, date of birth, usually also the sex; ESSENTIAL DOCUMENT according to ICH); EC guidelines request

that the participation of a patient is marked in the medical records; see INVESTIGATOR, PATIENT IDENTIFICATION LIST.

subject screening log syn. INTENT-TO TREAT LOG; to document subjects that entered pre-treatment screening but that did not receive the study medication; ("It may be relevant to provide the number of patients screened for inclusion and a breakdown of the reasons for excluding patients during screening …"; ESSENTIAL DOCUMENT according to ICH E3, Structure and content of clinical study reports).

substance see OLD SUBSTANCE.

substance master file see DRUG MASTER FILE.

substance name see INTERNATIONAL NON-PROPRIETORY NAME.

substantial amendment Changes to a clinical trial protocol that may have an impact on safety and/or the scientific value of a trial; these are e.g., changes in safety, selection criteria, value of the trial (e.g., endpoints), risk-benefit, quality of the IMP, management or conduct (e.g., reduced monitoring, new project manager), principal investigator or coordinating investigator, investigational sites etc.; see also AMENDMENT.

substantial evidence FDA: "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed LABELLING".

summary of pharmacovigilance system (SPS) Pre-inspectional form of the MHRA.

summary of product characteristics (SPC, SmPC) syn. data sheet; general information for prescribers on the correct use of a DRUG including RISKS; necessary for marketing authorisation within the EC and annexed to the PERIODIC SAFETY UPDATE REPORT; the SmPC includes the name of the proprietary product, qualitative and quantitative composition (ingredients, excipients), international nonproprietary name, the pharmaceutical form, pharmacological properties, therapeutic indications and contra-indications, warnings, shelf-life, storage conditions, and other particulars, and is part of module 1 of the CTD; see also COMPANY CORE DATA SHEET, COMPANY CORE SAFETY INFORMATION, PATIENT INFORMATION LEAFLET, QRD-FORMAT; for other types of documents see REFERENCE SAFETY INFORMATION.

sunset clause Marketing authorization of a product expires if the medicinal product is not on the market within 3 years of granting; see also RENEWAL.

supplementary protection certificate (SPC) Certificate for extending patent life of innovative pharmaceutical products, based on the date of their first marketing authorisation; (e.g. for additional 5 years in US, Japan) usually up to a total length of 14 years; in EC countries products can get a 5 year certificate, and a 15 years protection period; transition periods are variable and start between 1 January 1982 and 1 January 1988; there is no unitary European SPC, but national ones only, although harmonization is progressing.

supportive data Information on efficacy and safety not accepted as PIVOTAL and therefore not central to NEW DRUG APPLICATION.

suppressor gene A gene that can reverse the effect of a mutation in other genes.

suprabioavailability The new product displays a BIOAVAILABILITY appreciably larger than the approved product; reformulation to a lower dosage strength assuring THERAPEUTIC EQUIVALENCE will be necessary; see also PHARMACOKINETIC.

surface see BODY SURFACE.

surrogate FDA: non-clinical measure that can reliably predict clinical changes within a reasonable amount of time; see also BIOMARKER, OUTCOMES RESEARCH, SURROGATE ENDPOINT, SURROGATE MARKER.

surrogate endpoint = substitute/prognostic parameter for a clinical endpoint; instead of the (clinical) event itself an event directly related to it is recorded that indicates presence or worsening of a clinical condition in a clinical trial, e.g. cataract surgery instead of the diagnose cataract, dispensing of an antidepressant for depressive illness, specific markers or abnormal lab values reflecting progress, a.s.o.; s.e. are measured to get faster results in CLINICAL TRIALS, whereby the presence in a high percentage of the patients is a prerequisite; surrogate endpoints are frequently used in early phase of clinical development, e.g., PHASE IIa; see also ACCELERATED APPROVAL PROGRAM, SURROGATE, SURROGATE MARKER.

surrogate marker Measurement of a biological variable instead of the clinical condition, e.g. Magnetic Resonance Imaging instead of patient's disability in multiple sclerosis, tumour markers instead of lesions, forced expiratory volume in 1 s/FEV1 in lung diseases, CRP or ESR in inflammatory diseases; see also BIOMARKER, SURROGATE ENDPOINT.

surveillance active (e.g., post-authorisation safety study, registries, sentinel sites) or passive (spontaneous reporting) system for evaluating the safety of medicinal products; see EPIDEMIOLOGY, PHARMACOVIGILANCE, POST-AUTHORISATION SAFETY STUDY, PRESCRIPTION-EVENT MONITORING, REGISTRY, SIGNAL, SPONTANEOUS REPORTING.

survival analysis syn. life-table analysis; statistical technique for calculating the probability of developing a given outcome (death, relapse, medical intervention,

a.s.o.), taking into account the duration of follow-up; s.a. can be used to examine the distribution of time to occurrence of any DICHOTOMOUS outcome and applies to both observational and experimental clinical trials; most common methods of s.a. are the actuarial method and the Kaplan–Meier method; the actuarial method assumes a constant risk within (but not necessarily also between) each interval defining the life table, and computes cumulative survival rates for these regular time intervals in contrast to exact times as in the Kaplan–Meier method; the K.–M. method yields therefore a (less regular) curve with steps, each step representing the time of an "event" for each subject; the advantage of life-table a. is the possibility for calculating overall 5-year survival for an entire cohort even though only one patient was followed for 5 or more years; other methods to summarize survival are e.g. mean/median duration of survival, direct calculation of 1- or 5-year survival rates or events per person-year.

SUSAR Suspected Unexpected Serious Adverse Reaction; SUSARs have to be reported (whether occurring within the EC or outside) as soon as possible but not later than 7 calendar days after first knowledge by the sponsor, followed by a written report as complete as possible within 8 additional calendar days (total 15 days) to EMA (EudraVigilance) and Member States; the sponsor of a clinical trial is obliged to provide annually to authorities and ethics committees of EU member states a listing of all SUSARs that have occurred over this period and a report of the subjects safety (line-listings and aggregate summary tabulations by body systems, included in the development safety update report, DSUR); see ADVERSE REACTION, FDA 1639 FORM, UNLISTED ADVERSE DRUG REACTION.

sustained release see PROLONGED RELEASE, see also DRUG DELIVERY.

switch Change of the status of a drug from PRESCRIPTION ONLY MEDICATION to non-prescription drug (OVER-THE-COUNTER (OTC) drug).

symptoms Subjective indicators of a DISEASE as e.g. pain, tiredness, loss of appetite, anxiety a.s.o.; see also SIGNS.

symptom severity scale see COMPOSITE VARIABLE, GENIE SCORE, GLOBAL ASSESSMENT VARIABLE, VARIABLE.

synergism see EFFECT MODIFIERS, INTERACTION OF DRUGS.

systematic error see ERROR.

system-organ classes see medDRA, WHO ADVERSE REACTION TERMINOLOGY.

system-organ-class frequency (SOC) see WHO ADVERSE REACTION TERMINOLOGY.

system owner Person directly responsible for the functioning and maintenance of a system; see also PROCESS OWNER.

T

tablet see FORMULATION.

tablet excipients In addition to the active DRUG, MEDICINAL PRODUCTS often contain a number of other substances, e.g. for improving BIOAVAILABILITY such as DISINTEGRANTS (e.g. starch), for taste masking and lubrication to ease swallowing (e.g. coats of sugar, cellulose, polymers in film-coated tablets), or simply substances which facilitate production such as binders (e.g. cellulose derivatives), glidants (colloidal silica) or diluents (lactose, crystalline cellulose); see also FORMULATION.

tachyphylaxis Decreasing response to a DRUG with repeated doses; this develops, in contrast to TOLERANCE, within a very short time (min or h) as e.g. for histamine.

telomere Repetitive NUCLEOTIDE sequences at the end of a CHROMOSOME protecting the chromosome from damages resp. modifications and cells from senescence; as each cell division necessarily needs chromosome replication this protecting region progressively shortens with each cell division; without this protection APOPOTOSIS occurs; telomers can however be lengthened by an enzymes called telomerase, thus allowing cells to become potentially immortal as in cancer; telomerase seems to be involved also in chromosome repair; see ADVANCED THERAPY, PETO'S PARADOX.

temporality Exposure to a cause must precede the effect of the exposure.

termination visit syn. close out visit; last visit of a MONITOR or CLINICAL RESEARCH ASSOCIATE to a centre in order to collect all remaining CASE REPORT FORMS (CRF), drug samples, unused CRFs or CONSENT forms and usually also the INVESTIGATOR'S BROCHURE; at this occasion also financial and analysis/reporting aspects may be discussed with the trialist and her/his staff.

G. Nahler, *Dictionary of Pharmaceutical Medicine*,
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test article Any substance or device for human use which is subject to premarket approval; although regulations differ between countries most of them exclude e.g. cosmetics from national DRUG regulations.

test article accountability (TAA) American term for DRUG ACCOUNTABILITY.

test-retest Use of the same or questionnaire in the same patient at different periods of time to assess VALIDITY of measurement of exposure; see also FORWARD-BACKWARD TRANSLATION, VALIDATION.

therapeutic equivalent Dosage form exhibiting the same EFFICACY (toxicity) when administered in the same appropriate dosage regimen; EC: "A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and clinically shows the same EFFICACY and safety as that product, whose efficacy and safety has been established"; see also BIOLOGIC EQUIVALENT, ESSENTIALLY SIMILAR PRODUCT, PHARMACEUTICAL EQUIVALENT.

therapeutic index Ratio of the therapeutic dose (ED50) to the toxic dose (LD50); see also TOXICITY TESTS.

therapeutic potential Some health authorities provide ACCELERATED APPROVAL PROGRAMS for new DRUGS, depending on their therapeutic or innovative potential; for the FDA classification as "P" (priority) or "S" (standard) does exist; the therapeutic potential may be also important for price negotiations and REIMBURSEMENT; see also ACCELERATED APPROVAL PROGRAM.

therapy management see DISEASE MANAGEMENT.

three-way crossover design see CROSSOVER, DESIGN.

Threshold of Toxicological Concern (TTC) A general human exposure threshold value for chemicals below which no appreciable risk to human health is assumed despite the absence of chemical-specific toxicity data; currently set for toxic substance such as carcinogenic or mutagenic agents at 1.5 µg/person/day; see also TOXIC DOSE LEVEL, TOXICITY.

time-event schedule see FLOW CHART.

time trade-off (TTO) Technique for measuring UTILITY or QUALITY OF LIFE; patients are asked about the number of years in their present HEALTH state they would be willing to trade for a shorter life span in full health.

time-treatment interaction see CARRY-OVER effect.

tissue engineered product see ADVANCED THERAPY.

TNM-staging Stands for tumour-node-metastasis; widely used classification system of the Unio Internationalis Contra Cancrum, UICC (Union International contre le Cancer, Unio Internationalis Contra Cancrum) which is based on the size of the primary tumour T (To–no evidence of primary tumour, T4-tumour invades adjacent organs and vessels, TIS, Tx), degree of local spread to lymphnodes N (No–N3, N4 if applicable, Nx) and distant spread of metastases M (Mo–M1, Mx); histopathologic grading is also of prognostic importance (Histopathologic Grade G: Gx – grade cannot be assessed; G1 – well differentiated; G2 – moderately differentiated; G3 – poorly differentiated; G4 – undifferentiated); see also TUMOUR STAGING.

AJCC/UICC				Dukes
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	
Stage II	T3	N0	M0	B
	T4	N0	M0	
Stage III	Any T	N1	M0	C
	Any T	N2	M0	
	Any T	N3	M0	
Stage IV	Any T	Any N	M1	D

Dukes B, C is composed of better and worse prognostic groups

tolerance Reduction in the response of a drug treatment in a particular patient, e.g. by induction of enzymes as in the case of barbiturates; see also TACHYPHYLAXIS.

total organ carbon (TOC) Analysis of the Total Organ Carbon is a method used to test pure water and to validate it's quality or cleaning procedures; see also ALIMENTARY RISKS.

total quality management (TQM) In clinical research, TQM is ensured by strict adherence to "GXP" (GCP, GLP, GMP, …) including various additional standards such as e.g. ISO 9000 and EN 45000; see also QUALITY ASSURANCE.

toxic dose level (TDL) Lowest dose that produces haematological, chemical or other drug induced changes in the animal such that doubling the dose is not lethal; see also ALLOWED DAILY DOSE, NOEL, THRESHOLD OF TOXICOLOGICAL CONCERN.

toxicity tests Single dose t. (acute tests) are used to establish the lethal dose of a compound in at least two different species by at least two different routes of administration (incl. usually intravenously and route planned for application in

man); increasing doses are administered till an end-point, usually death, is reached; test animals are observed usually for a period of 14 but not less than 7 days; in repeat-dose t. (sub-acute t./less than 1 months duration, subchronic t. 1–3 months, chronic t./>3 months) the top dose is chosen so that it produces some minimal adverse effect (e.g. reduction in rate of body-weight gain) and dose/response relationship can be examined (two species of mammals, one of which must be a non-rodent); for products to be administered once only to humans, a test lasting 2–4 weeks shall be performed; reproductive toxicity t. investigate potential adverse effects during production and fertilization of gametes; embryo/foetal and perinatal t. investigates effects of a drug administered to the female during pregnancy or embryogenesis resp. ("fetal toxicity" or "teratology") or during birth and subsequent development; mutagenicity t. reveal changes in the genetic material of individuals or cells; carcinogenicity t. are normally required for substances likely to be applied in man longer than 3 months; intensive toxicity tests are especially important for products likely to be administered regularly over a prolonged time of a patient's life; as example for the correlation between planned duration of human treatment and necessary toxicity testing the following overview can be given:

Human treatment	Toxicity studies (in two species, one non-rodent)
One/several doses, 1 day	2 weeks
Repeated doses up to 14 days	4 weeks
Repeated doses up to 1 month	1 month
Up to 3 months	3 months
>3 months up to 6 months	6 months
Above 6 months	6 months

the FDA still requests 12 months chronic toxicity tests for drugs intended to be used for longer than 6 months; a complete toxicity program costs about five to ten million US$ and may use up to about 5,000 animals; see also CARCINOGENICITY TESTS, ECOTOXICITY, GENOTOXICITY, IMMUNOTOXICITY, LD-10, MAXIMUM TOLERATED DOSE, MINIMAL TOXIC DOSE, MUTAGENICITY TEST, NO-TOXIC-EFFECT-LEVEL, OLD SUBSTANCE, THERAPEUTIC INDEX, THRESHOLD OF TOXICOLOGICAL CONCERN; see also IN VITRO TOXICITY TESTING, STEM CELLS.

toxicokinetic Relates body drug concentrations and their kinetics to toxicological findings; see also IDIOSYNCRATIC REACTION.

trademark syn. proprietary name, brand name, invented name; may be the name of the manufacturer (opp. INTERNATIONAL NON-PROPRIETARY NAME, GENERIC NAME); a tm includes any word, name, symbol, device, or any

combination, used, or intended to be used, in commerce to identify and distinguish the goods of one manufacturer or seller from goods manufactured or sold by others, and to indicate the source of the goods; relates to a finished product and identifies the manufacturer; for a commercially available medicinal product; within the EC it is recommended to use the same t.m. throughout the Community, unless a justification to do otherwise is given; in most countries the t.m. is liable to revocation after 3–5 years of non-use. EMA states "if there is a minimum of 3 distinguishing letters, it is unlikely that it will be considered that there is a risk of confusion in writing" ("3-letter rule").

trade name Name used together with a trade mark; see TRADEMARK.

traditional herbal medicinal product EU: Medicinal product of herbal origin that has been in medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the European Community; claimed indications must be appropriate without the supervision of a medical practitioner; see also FUNCTIONAL FOOD, HERBAL DRUG, PHYTOMEDICINES, WELL-ESTABLISHED MEDICINAL USE.

transdermal delivery system (TDDS) syn.: transdermal delivery device (TDD); see DRUG DELIVERY, TRANSDERMAL PATCH.

transdermal patch Special formulation where the drug is absorbed through the skin, e.g. nitroglycerin, nicotin a.s.o.; in passive patches, the drug diffuses into the skin as a result of a gradient in either the drug concentration or solubility; in active patches, external forces are used; transdermal delivery is limited by the size of the drug (upper limit around 500 Da), the water and lipid solubility and the pharmacologically effective dose to be delivered; potential irritation/sensitisation of the drug towards the skin must be excluded; hair follicles can act also as an entry portal for both antigens and DNA to the skin; penetration enhancer are: liposomes and ethanol; physical methods are also used such as iontophoresis; see also CONTROLLED RELEASE, DRUG DELIVERY.

trans fats Fatty acids that contain "unsaturated" bonds between carbon atoms with ligands in "trans"-position (both ligands point in the opposite direction in contrast to the large majority of naturally occurring fatty acids with ligands in "cis"-position); the large majority of t.f. are of industrial origin; they are found in some margarines and "refined" oils but also in commercially baked products and deep fried fast food and are a major health concern; t.f. are known since 1911 (first patent for hydrogenated cotton seed oil); t.f. of food are incorporated into cell membranes affecting cell functions, and have been linked with many diseases such as coronary heart diseases, breast cancer (mortality rate in Western Europe ~175 per million) and diabetes (prevalence ~200,000 per million); in 1994, before restricting the content of t.f. in food by the FDA, it was

estimated that t.f. caused 20,000 deaths from heart diseases annually; many countries recommend a maximum limit of 2/100 g total fat/day, the WHO defined a population goal of less than 1 % of t.f. of overall energy intake; see also ALIMENTARY RISKS, ALLOWED DAILY DOSE, MAXIMUM RESIDUE LIMIT, PHARMACOVIGILANCE.

transgenic drug Drug (usually a protein) which is manufactured from transgenic animals (e.g. by introducing a human gene such as for antithrombin III in a cow which then excretes the drug with the milk); see BIOTECHNOLOGY, GENE THERAPY.

transition matrix Frequently used format for presentation of e.g. laboratory data (example given for a total of 170 subjects, x-axis: number of subjects with observations as specified after treatment, y-axis: number of observations before treatment); see also SHIFT TABLE.

	After			
Before	Lowered	Normal	Raised	Total
Lowered	9	5	0	14
Normal	27	29	14	70
Raised	0	45	41	86
Total	36	79	55	170

transplantation Over 28,000 human-to-human organ transplants were carried out in 2006 in the U.S (1994: 18,200); over one million people worldwide has received allograft organs and some of them have already survived more than 25 years; 5-years survival rates for most organ transplant programmes are around 70 %; the increasing demand for organs outstrips supply; see also ALLOGENIC, BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, BIOTECHNOLOGY, IMMUNOTHERAPY, XENOTRANSPLANTATION.

treatment emergent signs and symptoms (TESS) ICH: Signs and symptoms not seen at baseline (i.e. before starting a new treatment or a clinical trial) and that worsened even if present at baseline; see also ADVERSE DRUG REACTION.

treatment IND syn. treatment use, named patient use; FDA: "A t.IND is a special case of an IND (INVESTIGATIONAL NEW DRUG) where the only protocol under the IND is the treatment protocol. … A treatment protocol allows use … of a promising new agent directed primarily at patient care by physicians who agree to follow the PROTOCOL." t.IND criteria: treatment of a serious or immediately LIFE-THREATENING DISEASE, no satisfactory alternative treatment available, the drug is under investigation in a CONTROLLED CLINICAL TRIAL under an IND, SPONSOR is actively pursuing marketing approval; in contrast to a

COMPASSIONATE USE a t.IND is based on at least enough data to provide a reasonable expectation that the drug may be useful and will not be unduly harmful; the t. protocol or t.IND covers an unspecified number of patients (anyone meeting the entry criteria) which would not be the case with other protocols under an IND; see also EXPANDED-ACCESS PROGRAM.

treatment schedule Frequency with which a specific DRUG should be taken by patients, e.g. weekly, once daily to several times daily; this depends on how long the desired effect lasts which is very much depending on the HALF LIFE of the substance but also organ functions and the duration of the biological effect; see also LOADING DOSE, MAINTENANCE DOSE, PHARMACOKINETIC.

treatment use see TREATMENT IND.

trial see CLINICAL TRIAL.

trial design see DESIGN.

trialist see INVESTIGATOR

trial management organisation see CLINICAL RESEARCH ORGANISATION, SITE MANAGEMENT ORGANISATION.

trial master file (TMF) syn. clinical trial manual, project book note, study file; hard copy of all the documentation relating to a CLINICAL TRIAL; includes e.g. also AUDIT certificates and reports, DATA on ADVERSE EVENTS; a similar, widely overlapping file is held at the investigational site (Investigator's Site File-ISF).

tumour staging Classification systems used to describe size of a tumour and extent of disease; classification systems which are widely used are e.g. according Dukes, or the TNM- (UICC-, AJCC-) STAGING, FIGO-STAGING; see CLASSIFICATION OF RECURRENCE, DISEASE FREE INTERVAL, TMN-STAGING.

tumour suppressor gene Any of a category of genes that can suppress transformation or tumorigenicity (probably ordinarily involved in normal control of cell growth and division).

turbo-haler see POWDER INHALER.

two-stage design see GEHAN'S DESIGN.

two-tailed test syn. two-sided t.; opposite: ONE-TAILED T.; used to detect differences in either of two directions (e.g. experimental treatment is either superior or worse than control treatment); a two-tailed t. is most appropriate when the two treatments are roughly equivalent (e.g. in terms of risks or costs); two-tailed t. require larger sample sizes.

two-way crossover design see CROSSOVER, DESIGN.

type I error see ALPHA ERROR.

type II error see BETA ERROR.

type of reaction see ADVERSE REACTION.

type IA variation (type IA notification); variation to a marketing authorisation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned ("do and tell"; e.g., typographical changes which are otherwise non-consequential to the main change; "administrative changes"; contact details of the MA holder; up to tenfold increase/decrease of batch size; tightening of in-process limits); variations can be grouped whereby the further process is depending on the change(s) with the highest impact; changes can be grouped and submitted within 12 months, including the date of implementation of each variation; there are also Type IA variations with immediate notification ("Type IAin") e.g., change of address of MA holder, manufacturer; switch to the "Summary of the PV System + PV Master File" (replacing the "Detailed Description of the PV System", DDPS); see also EXTENSION APPLICATION.

type IB variation variation to a marketing authorisation which neither IA nor II nor an extension ("tell, wait 30 days, and do"), e.g., more than tenfold increase compared to the currently approved batch size; addition or replacement of a specification parameter as a result of a safety or quality issue; harmonisation of the patient information leaflet (PIL) across all member states for a MR product is also a Type IB variation; the applicant must include a detailed justification to his submission why he considers the variation as Type IB; if within 30 days following the acknowledgement of receipt of a valid notification, the competent authority of the reference Member State has not sent the holder an unfavourable opinion, the notification shall be deemed accepted by all relevant authorities; see also EXTENSION APPLICATION.

type II variation variation to a marketing authorisation not deemed to be minor (type IA and IB), e.g. a new PHARMACOVIGILANCE system, new indication, modification of the SPC on safety/efficacy information, new manufacturer of the API or other substantial changes to the manufacturing process a/o specification; in case of an urgent safety restriction (USR), a "Safety Variation Application" must be submitted within 15 days after the initiation of the USR; for fees see EUROPEAN MEDICINES AGENCY; see also EXTENSION APPLICATION, URGENT SAFETY RESTRICTION.

type III error see GAMMA ERROR.

U

unblinded study syn. open s.; study where both physician and patient know the treatment; see DESIGN, OPEN STUDY.

uncontrolled study Study without CONTROL group (automatically also not blinded), e.g., as pilot study for collecting very first experiences or as open extension or follow-up study of a controlled clinical study; see also DESIGN.

underweight see CACHEXIA, WEIGHT, see also ADVERSE REACTION.

undesirable effect see ADVERSE DRUG REACTION, SIDE EFFECT.

unexpected adverse event ICH: "… is one, the nature or severity of which is not consistent with information in the relevant SOURCE DOCUMENT(s). Until source documents are amended, EXPEDITED REPORTING is required for additional occurrences of the reaction".

Uniform Requirements for Manuscripts Submitted to Biomedical Journals see: http://www.icmje.org/urm_main.html; see also REPORT

Union Reference date see: European Union Reference Date.

Unique Device Identification (UDI) Barcode-based system for the identification of a specific MEDICAL DEVICE.

Unit of Pulmonary Toxicity Dosage (UPTD) to predict pulmonary damage after prolonged oxygen therapy; 1 min of 100 % oxygen at 1 atmosphere is equivalent to 1 UPTD; a UPTD of 1,425 will produce a 10 % reduction in the vital capacity which is the maximum acceptable reduction.

unlicensed medicine Term for use of a drug that may have a marketing authorization outside but not within the European Community; the term overlaps with "unlicensed use" or MISUSE; see also OFF-LABEL USE.

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unlicensed use Medicinal product that has no marketing authorization or no marketing authorization in the respective indication or population; see also OFF-LABEL USE, UNLICENSED MEDICINE.

unlisted adverse drug reaction ICH: "An ADVERSE REACTION, the nature or severity of which is not consistent with the information included in the COMPANY CORE SAFETY INFORMATION"; see also LISTED ADVERSE DRUG REACTION, SUSAR-Suspected Unexpected Serious Adverse Reaction.

urgent amendment Term used for changes in CLINICAL TRIALS, see AMENDMENT.

urgent safety restriction (USR) direct provision of safety information to patients about an identified risk without delay ("Rapid Alert", through national media such as newspapers, electronic media, …); de facto it is an interim change to product information concerning one or more of the following items in the SUMMARY OF PRODUCT CHARACTERISTICS, the indications, posology, contraindications, warnings, target species and withdrawal periods due to new information having a bearing on the safe use of the medicinal product (Eudrax Vol.2, chap.5); may be imposed by the marketing authorization holder or by the competent authority; If no objections have been raised by the relevant authority within 24 h following receipt of that information, the urgent safety restrictions are deemed as accepted; changes will subsequently be introduced via a corresponding variation in the marketing authorisation; an USR may have important consequences such as the recall of the medicinal product from the market, suspension, withdrawal of the marketing authorization etc.; see also BLACK TRIANGLE, LEGAL STATUS, SAFETY ALERT, TYPE II VARIATION.

utilisation study see PHARMACOEPIDEMIOLOGY.

utility measurement Economic perspective of QUALITY OF LIFE measurements; u. reflects here the degree of satisfaction or amount of well-being of a patient with a specific treatment, independent of what the treatment actually costs or whether it produces any financial gain; u. is standardized relative to states of HEALTH and provides a synthetic assessment of QUALITY OF LIFE; it takes into account patient's preferences which are translated into monetary terms esp. costs (for visits, hospitalizations, lab tests, additional drugs or treatments, days out of work; different rating methods can be used to obtain utility values (e.g. TIME TRADE-OFF, STANDARD GAMBLE, WELL-BEING SCALE); see also COST/UTILITY ANALYSIS, QUALITY-ADJUSTED LIFE-YEARS.

V

vaccine A preparation that contains an antigen consisting of whole disease-causing organisms (killed or weakened), or parts of such organisms, and is used to confer immunity against the disease that the organism cause. Vaccine preparation can be natural, synthetic, or derived by recombinant DNA technology; v. are agents stimulating an immune response for prophylactic or therapeutic purposes; several types of vaccines are known, e.g. subunit v. (without the potential dangers of incompletely killed pathogens or attenuated strains that have reverted to a virulent state), peptide v. (contain several antigen determinants), DNA v. (contain gene-encoding antigens), vector v. (live, nonpathogenic viruses with antigen genes inserted into the viral genome); see also ADJUVANT, LARGE SIMPLE TRIAL DESIGN, NON-INTERVENTIONAL STUDY.

validation EC: "action of proving, in accordance with the principles of GOOD MANUFACTURING PRACTICE, that any procedure, process, equipment, material, activity or system actually leads to the expected results"; FDA "documented evidence and assurance that computer systems that touch a process perform in a reliable and repeatable manner" (21 CFR 11); see also COMPUTERISED SYSTEM, QUALIFICATION.

valid case analysis (VC-analysis) syn. PER-PROTOCOL A; see ACTUAL-TREATED A., ANALYSIS OF STUDY RESULTS, EXPLANATORY TRIAL, INEVALUABILITY RATE.

validity Extent to which an instrument (test) measures what is intended to be measured (agreement between the measure and the "true" value or a designated "gold" standard or criterion resp.); when evaluating v. three aspects should be considered: criterion v., which refers to the extent that the same results as a gold standard are produced, content v., which refers to the judgement that the items included in the scale are representative of the domain measured, and construct v., which refers to the variation explained

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by other constructs or tests; usually a test is only valid with respect to a specific purpose, range, and sample; external v. = degree to which results valid in one population can be generalized to another; internal v. = extent to which the analytic inference derived from the study sample is correct for the target population (extent to which the results of a study are impaired by analytic BIAS); see also CONSTRUCT VALIDITY, MEASUREMENT PROPERTIES, QUALIFICATION, RELIABILITY, TEST-RETEST.

Vancouver style of citation Health authorities, but also many scientific journals have agreed to accept papers submitted according to the format described in the "Vancouver Declaration" of 1997; see paper: "Uniform requirements for manuscripts submitted to biomedical journals" BMJ 1991, 302: 338–34. Examples of citations: (i) Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B for the Austrian Immunoglobulin in Multiple Sclerosis Study Group: Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Lancet 1997; 349: 589–593. (ii) Nahler G: International medical device registration - Austria, in Donawa ME, eds: International Medical Device Registration. Buffalo Grove, IL, Interpharm Press, 1996, pp 33–58. See also HAVARD STYLE.

variability Often used synonymously to REPRODUCIBILITY and PRECISION; extent of differences between repeated measurements; v. results from alterations of measurement conditions as (inter/intra-) observer ERROR, machine error, timing of outcome measures, population differences a.s.o.; see also ACCURACY, CLINICAL HETEROGENEITY, CONFIDENCE INTERVAL, MEASUREMENT PROPERTIES, MEDICAL CULTURE.

variable syn. parameter; event, characteristic or attribute that is measured in a study; see COMPOSITE VARIABLE, CONFOUNDER, COVARIATE, DATA, GLOBAL ASSESSMENT VARIABLE.

variance Describes the spread (variability) of MEASUREMENTS; e.g. differences among SUBJECTS within the same group (intragroup v.); square of the STANDARD DEVIATION (SD × SD); see also REPRODUCIBILITY, VARIABILITY, VARIATION.

variation see COEFFICIENT OF VARIATION.

variation procedure Variations are changes to the marketing authorization of a medicinal product; they can be classified in different categories, depending on the level of risk, the impact on safety, efficacy and quality; see EUROPEAN MEDICINES AGENCY, EXTENSION APPLICATION, TYPE IA VARIATION, TYPE IB VARIATION, TYPE II VARIATION.

Vidal French drug list; see NATIONAL DRUG LIST.

Vigibase™, see WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING.

Vigimed™ e-mail-based system for information exchange between the countries participating in the WHO Programme for International Drug Monitoring; see WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING.

virus A submicroscopic organism that contains genetic information but cannot reproduce itself. To replicate, it must invade another cell and use parts of that cell's reproductive machinery.

visit log list syn. MONITORING LOG LIST; list in which the date of each visit of the MONITOR/CLINICAL RESEARCH ASSOCIATE at the trial site is entered (usually by the trialist).

visual analogue scale (VAS) syn. linear analogue self assessment (LASA); scale with finite boundaries at 0 and 100 mm (end of the scale) for the conventional 10 cm line presentation; in general such scales are more reliable and sensitive but also more difficult to explain to patients than e.g. a Numerical Pain Scale (NPS, discontinuous 0–10 data collection between the same boundaries) ORDINAL SCALES; an "anchored" or "categorized" VAS has the addition of one or more intermediate marks positioned along the line with reference terms assigned to each mark to help subjects to identify the locations between the ends of the scale; see also QUALITY OF LIFE SCALE, SCALE.

vital signs syn. vital parameters; basic parameters describing the physiological status are: blood pressure, heart – and respiratory rate, body temperature.

volume of distribution (Vd) Apparent (hypothetical) volume of body fluid (given in L or L/kg) into which a DRUG would distribute at equilibrium; Vd = dose (mg/kg)/peak concentration (mg/L)=L/kg; the Vd does not represent a real volume but is rather the size of the pool of body fluids that would be required if the drug behaves as ideal drug and is distributed equally throughout all portions of the body; the Vd cannot (theoretically) exceed total BODY WATER and is markedly effected by the binding of the drug, e.g. to serum proteins but also by the proportion of body fat, sex, subject's age, and disease; when the Vd is large, the tissue concentration is also large and the plasma concentration small; when the Vd is small, most of the drug remains in the plasma; Vd can be used to estimate peak blood concentrations and the amount of drug ingested in case of intoxication; see also ADME, GERIATRIC EVALUATIONS, PHARMACOKINETIC.

volunteer A subject participating in a PHASE I clinical trial is usually called a healthy volunteer.

voluntary reporting (VR) see YELLOW CARD.

vulnerable subject syn. incapacitated and/or protected subjects; ICH: "Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation … of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases/lack of alternative treatment(s), persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving (legally acceptable) consent"; other specific vulnerable populations include (EUDRACT): women of child bearing potential, pregnant or nursing women.

W

waist circumference Circumference around the bare abdomen, just above the hip bone (parallel to the floor, exhaled); excess weight, as measured by BMI, is not the only risk to health but the location of fat. Fat mainly around the waist is more likely to cause health problems than if localised mainly in hips and thighs. This is true even if the BMI falls within the normal range. Women with a waist measurement of more than 90 cm or men with a waist measurement of more than 100 cm may have a higher disease risk than people with smaller waist measurements; see also ANTHROPOMETRY, OBESITY, WAIST-HEIGTH-RATIO, WAIST-HIP-RATIO.

waist-height-ratio (WHtR) Independent of age, the ratio of waist size to height is considered a reliable indicator for risks linked to obesity, better than the BMI, waist-to-hip-ratio or the waist circumference; risks decrease proportionally to the ratio with only little differences between genders and populations of different ethnic groups: a WHtR <50 % is generally considered healthy; risks increase substantially >55 %;

	Women	Men
Extremely slim	35–42	35–43
Slender and healthy	42–46	43–46
Healthy, normal, attractive	46–49	46–53
Overweight	49–54	53–58
Obese, seriously overweight	54–58	58–63
Highly obese	>58	>63

see also ANTHROPOMETRIC MEASUREMENTS, BODY MASS INDEX, BROCA-FORMULA, LORENTZ-FORMULA, WAIST CIRCUMFERENCE, WAIST-HIP-RATIO, WEIGHT.

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waist-hip-ratio In adults above 70 years, the ratio of waist size to hip size may be a better indicator for risks linked to obesity than the BMI or the waist circumference. According to WHO, abdominal obesity is defined as w/h ratio >0.80 in women and >0.95 in men. In women, each 0.1 increase in the waist-hip ratio is associated with a 28 % relative increase in mortality rate (the number of deaths per 100 older adults per year); in men, the rate of dying was 75 % higher for a waist-hip ratio >1.0 – that is, men whose waists were larger than their hips - relative to those with a ratio of 1.0 or lower; according to the WHO, the risk increases if the waist measurement exceeds 94 cm (37 in.) for men and 80 cm (32 in.) for women; in women, the w/h ratio correlates strongly with fertility; a ratio of 0.70 reflects optimal oestrogen levels; women should aim for a waist circumference of no greater than 80 cm (32 in.) and men should aim for no greater than 94 cm (37 in.); see also ANTHROPOMETRIC MEASUREMENTS, BODY MASS INDEX, BROCA-FORMULA, LORENTZ-FORMULA, WAIST CIRCUMFERENCE, WAIST-HEIGHT-RATIO, WEIGHT.

waiver Acceptance by the FDA of a procedure at variance with their regulations.

wash-out period Period after stopping a treatment with a DRUG and in which the patient usually undergoes no further therapy; this allows previous drug or treatment effects to dissipate before a new treatment starts (normally about five times the half-life); see also RUN-IN PHASE.

Web-based data entry Data is transacted and stored directly, online, and in real-time, on a server via the internet, usually at the sponsor or CRO facility; thus, separate source data may be necessary; usually there is no e-DC specific software installed on the local computer of the investigator; see also DATA ENTRY, ELECTRONIC DATA CAPTURE, REMOTE DATA ENTRY.

Wei-Lachin procedure Statistical test procedure, based on the Wilcoxon-Mann–Whitney test, that allows use of multiple endpoints; see also O'BRIAN PROCEDURE, PRIMARY ENDPOINT.

weight A number of different indices are in use to describe the relationship between weight (body mass) and height in order to allow categorisation of subjects according to obesity (thin: ≤80 % of the standard of a population, underweight ≤90 %, overweight ≥110 %, obese ≥120 %, superobese >159 %, and morbid obesity >200 %); w. changes ≥7 % are considered as abnormal; an adult who has a BMI between 25 and 29.9 is considered overweight (≥30 obese); see also ANTHROPOMETRIC MEASUREMENTS, BODY COMPOSITION, BODY-MASS-INDEX (QUETELET'S INDEX), BROCA-FORMULA, CACHEXIA, LORENTZ FORMULA, ROHRER INDEX.

weighted average Gives different weights to each component of the average.

welfare External factors, e.g. duration of hospitalisation, need for assistance in daily life activities, consumption of medicines, length of sick leave a.s.o., influencing QUALITY OF LIFE.

well-being Exclusively subjective parameter which reflects the individual's own qualitative evaluation of his/her physical and/or mental condition often in relation to treatments; see also QUALITY OF LIFE.

well-being scale Instrument for UTILITY MEASUREMENTS; patients are asked a number of questions about their function and are then classified into one of a number of categories on the basis of their responses; each category has a value assigned to it that has been established in previous ratings by another group (e.g. a random sample of the general population); see also HEALTH PROFILE, QUALITY OF LIFE SCALE.

well-established medicinal use EC: Refers to medicinal products with "a recognized efficacy and an acceptable level of safety by means of a detailed scientific bibliography"; the period of time for establishing a "well-established use" may differ between products but must not be less than 10 years from the first systematic and documented use of that substance in the EC; a detailed description of the strategy used for the search of published literature and justification for inclusion of references in the application is required; see also APPLICATION, TRADITIONAL HERBAL MEDICINAL PRODUCT.

wetting agent see EXCIPIENTS.

white-coat hypertension About 20 % of patients with persistently raised blood pressure are normotensive when their blood pressure is measured away from physician's room; see also HAWTHORNE EFFECT, PLACEBO EFFECT.

WHO-adverse reaction dictionary (WHO-ARD) Computerised dictionary; see WHO-ADVERSE REACTION TERMINOLOGY.

WHO-adverse reaction terminology (WHO-ART) Created 1968; open-ended terminology for coding of adverse reaction terms; it exists in several languages and is used by drug regulatory agencies and pharmaceutical companies, with new terms added as necessary; WHO-ART is built up as a tree structure ("system-organ class", "high level term", "preferred term"); it comprises approx. 1,600 preferred terms, i.e., terms used to describe adverse drug reactions reported to the WHO system; input to computer files is usually made at the preferred term level; synonyms to preferred terms are often provided by the reporting site and are included at the input side ("included terms" around 2,000) in order to find the right preferred term more easily; terms pertaining to the

same body organ are grouped into a system-organ class, e.g. cardiovascular system, respiratory system a.s.o. whereby a preferred term can be allocated up to a maximum of three different system-organ classes; system-organ classes are groups of adverse reaction preferred terms pertaining to the same system-organ; they are used on the output side; all together over 30 system-organ classes exist; preferred terms are grouped into high level terms (approx. 150) which are more general terms for qualitatively similar conditions (e.g., thrombophlebitis leg and thrombophlebitis arm represent two different preferred terms but are grouped under thrombophlebitis as a high level term and are grouped under "cardiovascular system disorders" and/or "platelet, bleeding and clotting system" and/or "vascular (extracardial) system" as system-organ class); the WHO-ART is the basis for an index (WHO-Adverse Reaction Terminology List) with 7-digit CODES, 1–4: preferred term, 5–7: included term with up to 3 organ classes (4 digits) for each ADVERSE REACTION; preferred terms (PT) are always assigned the sequence number 001, included terms (IT) get the same record number as their preferred terms, but with a higher sequence number 00n; a high level term (HLT) is always in itself also a preferred term; example: acidosis: the PT has the adverse reaction number (ARECNO) 0363 001, IT are acidosis metabolic with the ARCNO 0363 003, or bicarbonate reserve decrease with the ARECNO 0363 004, the HLT is acidosis with the high level link 0363; see also MedDRA.

WHO-adverse reaction terminology list (WHO-ARTL) see WHO-ADVERSE REACTION TERMINOLOGY.

WHO collaborating centre for international drug monitoring System for collecting spontaneous reports on adverse reactions (Vigibase™) which are sent by the physician (also dentist or coroner) or company to national centres, usually health authorities, and by them at 3 month intervals, to the WHO Collaborating Centre in Uppsala; each year the centre receives about 200,000 AE-reports; up to now, this system which started in 1968, operates in more than 90 countries, mainly in Europe (e.g. in GB, S, N, D); number of reports/million inhabitants and year are quite different: around 200–400 in Denmark in comparison with 10–20 in Italy; reporting by pharmaceutical companies is based on the CIOMS-FORM of adverse reactions; other regulatory report forms are the FDA 1639 (US) and the "yellow card" of the Committee on Safety of Medicines (CSM) in UK; other accessible databases are e.g., the Canada Vigilance Adverse Reaction Online Database, or the Adverse Events Reporting System database of the FDA or EMA's "European Database of Suspected Adverse Reaction Reports" (www.adrreports.eu); see also YELLOW CARD PROGRAMME.

WHO-drug dictionary (WHO-DD, WHO-ATC/DDD Index, former Drug Reference List); index of all drug names and substances that is based on the

Anatomical Therapeutic Chemical (ATC) classification system and the DEFINED DAILY DOSE (DDD); in 2008 the dictionary contained 194,885 unique names, 1,472,631 different medicinal products, trade names with for example form and strength information added and 10,049 different ingredients mentioned in these products; a computerised dictionary is available on magnetic tape or diskette; updatings are on a quarterly basis; other coding systems for drugs are e.g., the National Drug Code of the US; see also WHO-DRUG REFERENCE LIST.

WHO-drug reference list (WHO-DRL) see WHO Drug Dictionary; Printed version of the WHO-DRUG DICTIONARY with a cross index of all DRUG names and substances listed in alphabetical order which have occurred on ADVERSE REACTION reports submitted to the WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING from 1968 onwards; it includes by 1992 26,750 different drug trade names of which 10,426 are multiple ingredient drugs; this corresponds to over 7,000 chemical substances; about 2,000 drug names are added yearly; the WHO-DRL is issued annually.

WHO-essential drug list (WHO-EDL) Contains more than 280 drugs either in the main listings or as"complementary" drugs, i.e. drugs which can be used because drugs on the main list cannot be made available or are known to be ineffective/inappropriate in a given individual (e.g. reserve antibiotics) or which are used in rare disorders or in exceptional circumstances.

wholesale distribution "All activities consisting of procuring, holding, supplying or exporting medicinal products apart from supplying medicinal products to the public" (Dir 2001/83/EC); see also LICENCE HOLDER.

wholesaler see WHOLESALE DISTRIBUTION.

WHO performance status scale syn. ECOG-Zubrod scale; see PERFORMANCE STATUS; see also ORDINAL SCALE.

WHO-toxicity scale A 5-grade system (0–4) for reporting of acute and subacute toxic effects of cancer treatment.

willingness to pay (WTP) Maximum amount that a person is willing to pay to achieve a particular good health state or outcome, or to avoid a particular bad health state or outcome, or to decrease its probability; see ECONOMIC ANALYSIS.

withdrawals (1) Subjects not finishing a CLINICAL TRIAL for study related reasons and which are therefore excluded by the trialist, e.g. due to ADVERSE EFFECTS, treatment failure or deterioration of patient's condition resp. or major PROTOCOL violations, e.g. NONCOMPLIANCE, "no-shower" for clinical appointments, pregnancy or other conditions which render patients ineligible, included

because they were already ineligible to enter and should have been excluded initially; together with DROPOUTS they represent a considerable source of BIAS in a trial; a standard "withdrawal form" exploring reasons and circumstances should therefore be an integral part of each CRF; there should always be a follow-up of patients withdrawn; furthermore statistical analysis should include all subjects entering a study (INTENT-TO-TREAT principle); see also DISCLOSURE PROCEDURE, LOSS TO FOLLOW-UP, RUN-IN PERIOD; (2) pharmaceutical products withdrawn from sale (voluntary) or MA has not been renewed or revoked; between 1961 and 2007 at least 120 drugs have been withdrawn for safety reasons (about 2–7 per year, 50 % within 5 years post marketing authorization); in the EC (EMA), a total of 31 medicinal products was withdrawn or MA was not renewed between 2001 and 2005; according to the FDA (CDR annual national report), a total of 2,790 prescriptions and 818 over-the-counter (OTC) drugs were withdrawn during the last 10-year period from 1996 to 2005; see also CESSATIOM OF PLACING ON THE MARKET, REBOUND EFFECT, RECALL, SANCTION.

withdrawal (**substance**) DSM-IV-TR criteria for a substance withdrawal disorder include the following elements: (1) the development of a substance-specific syndrome due to abrupt cessation or reduction in use; (2) the syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; (3) the symptoms are not due to a general medical condition and are not better accounted for by another mental disorder; MAH must continue to report adverse reactions and to submit PSURs (subject to agreements with the health authority); see DEPENDENCY (physical), MARKETING AUTHORIZATION HOLDER (MAH), REBOUND EFFECT.

withdrawal trial see DESIGN.

within-subject design syn. within patient comparison, intra-individual comparison; opp. between-subject d.; each subject (patient) serves as his own control, e.g. in CROSS-OVER D. or SINGLE CASE studies; furthermore measuring changes from baseline (RUN-IN PHASE) usually reduces drastically the number of patients required, e.g. pretreatment blood pressure measurements in anithypertensive trials; see also DESIGN.

women Most drug laws regulate the inclusion of w. in CLINICAL TRIALS, discouraging recruitment in child bearing age, at least until teratogenicity data from animal studies are available; revised NIH-guidelines (1994) require among others that "women and minorities and their subpopulations are included in all human subject research", and that they are "included in phase III clinical trials so that valid analysis of differences in intervention effect can be performed"; most laws require now pregnancy testing before and in regular intervals, verification of contraceptive use, and detailed information in the INFORMED

CONSENT procedure; despite gender differences in drug action, analyses of data by sex are still rarely requested; see also LABELLING, PREGNANCY OUTCOME, VULNERABLE SUBJECT.

work breakdown structure (WBS) Hierarchical organisation of tasks; see also PROJECT MANAGEMENT.

work(ing) instructions see STANDARD OPERATING PROCEDURES.

World Health Organisation (WHO) Currently more than 180 states are members of the WHO.

X

xenotransplantation Animal-to-human organ or tissue transplantation, may also include materials of transgenetically-altered animal donors (e.g. pigs) as alternative source to human organs; there may be some risk of transmitting hitherto unknown xenogeneic diseases to the recepient but also for the population at large; see also BIOLOGICAL MEDICINAL PRODUCT, BIOPHARMACEUTICAL, BIOTECHNOLOGY, IMMUNOTHERAPY, TRANSPLANTATION.

xenogeneic disease Animal-to-human transmitted disease; see also SECONDARY ATTACK RATE, XENOTRANSPLANTATION.

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Y

yellow card programme Reporting of suspected ADVERSE REACTIONS to drugs in the UK; SPONTANEOUS REPORTING SCHEME (reporting primarily by patients in contrast to active DRUG SAFETY MONITORING, PRESCRIPTION-EVENT MONITORING by health professionals) established 1964 and operated by the MHRA in UK; the system is completely voluntary whereby physicians but also dentists, coronors and patients are encouraged to report (other countries accept only reporting of side effects by health care professionals); incomplete information provided often limit it's use; other reporting systems are e.g., the Canadian Adverse Reaction Monitoring Program (CADRMP) or the Adverse Event Reporting System (AERS) of the U.S.; see also BLACK TRIANGLE, CASE-CONTROL STUDY, EPIDEMIOLOGY, EUDRAVIGILANCE, MEDWATCH, PHARMACOVIGILANCE, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING.

Yule's Q ratio see DISPROPORTIONALITY ASSESSMENTS.

Yule-Simpson effect see SIMPSON'S PARADOX.

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Z

zero order kinetics see KINETIC.

Zubrod performance status syn. WHO performance status scale; see PERFORMANCE STATUS.

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Abbreviations/Acronyms

AA	Application Area
a¯a¯	ana partes aequales (to identical parts)
AAA	(1) Acute Anxiety Attack; (2) Alcoholics Anonymous Association; (3) Abdominal Aortic Aneurysm
AAC	Antibiotic-Associated Colitis Application
AADA	Abbreviated Antibiotic Drug Application (FDA)
AAMI	Association for the Advancement of Medical Instrumentation (US)
AAPCC	American Association of Poison Control Centers (US)
AAPP	American Academy of Pharmaceutical Physicians (US)
AAPS	American Association of Pharmaceutical Sciences (US)
Ab	(1) Antibody; (2) Abortus
ABEMIP	Association Belge des Médecins de l'Industrie Pharmaceutique (also BEVAFI) (Belgian society of physicians in the pharmaceutical industry)
ABHI	Association of British Health-Care Industries
ABMT	Autologous Bone Marrow Transplant
ABP	Arterial Blood Pressure
ABPI	Association of the British Pharmaceutical Industry
AC	Ante cibos (medication to be taken before meal)
ACCME	Accreditation Council for Continuing Medical Education (US)
ACE	Angiotensin-Converting Enzyme
ACPP/ACMIP	Association of Canadian Pharmaceutical Physicians/ Association Canadienne des Médecins de l'Industrie Pharmaceutique
ACRPI	Association for Clinical Research in the Pharmaceutical Industry
AD	(1) Alzheimer's Disease; (2) Arteriosclerotic Disease; (3) Atopical Dermatitis
ADD	Attention Deficit Disorder

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ADE	(1) Adverse Drug Event, Adverse Drug Experience; (2) Acute Disseminated Encephalitis
ADEPT	Antibody-Directed Enzyme Prodrug Therapy
ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, Excretion
ADP	Automated Data Processing
ADPL	Average Daily Patient Load
ADR	Adverse Reaction, Adverse Drug Reaction
ADRAC	Adverse Drug Reactions Advisory Committee
ADROIT	Adverse Drug Reaction On-line Information Tracking (UK)
ADRRS	Adverse Drug Reaction Reporting System
ADs	Advertisements
AdS	Académie des Sciences (France)
ADT	(1) Alternate Day Treatment; (2) Accident du Travail
AE	Adverse Event, Adverse Experience
AEAIC	Académie Européenne d' Allergologie et Immunologie Clinique
AED	Anti-Epileptic Drug
AEFI	(Association of Industrial Pharmacists, Spain)
AERS	Adverse Events Reporting System (FDA)
AESAL	Académie Européenne des Sciences, des Arts et des Lettres
AESGP	Association Européenne des Spécialités Pharmaceutiques Grand Public (European Proprietary Medicines Manufacturers' Association, Paris)
AF	Atrial Fibrillation
AFAQ	Association Française pour l'Assurance Qualité (French Association for Quality Assurance)
AFEC	Association Française pour l'Etude du Cancer (Paris)
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (renamed in 2012 to Agence Nationale de Sécurité du Médicament ANSM)
AIFA	Agenzia Italiana del Farmaco (Italian health authority)
Ag	Antigen
AGIM	Association Générale de l'Industrie du Médicament
AHA	(1) American Heart Association; (2) Area Health Authority
AHCPR	Agency for Health Care Policy and Research (US)
AHF	Antihaemophilic Factor
AHRQ	Agency for Healthcare Research and Quality (USA)
AI	Artificial Intelligence
AICRC	Association of Independent Clinical Research Contractors
AIDS	Aquired Immune Deficiency Syndrome
AIFA	Agenzia Italiana del Farmaco (Italian Drug Agency)
AIM	Active Ingredient Manufacturer

AIMD	(1) Active Implantable Medical Device; (2) Active Ingredient Manufacturer
AIMS	Arthritis Impact Measurement Scale
AINS	Anti-inflammatoire Non-Stéroidique (= NSAID)
AJCC	American Joint Committee on Cancer
AL	Acute Leukaemia
ALARA	As Low As Reasonably Achievable
ALGOL	Algorithmic Language
ALI	Annual Limit of Intake
ALL	Acute Lymphatic Leukaemia
ALS	Amyotrophic Lateral Sclerosis
a.m.	(1) ante meridiem (before noon); (2) ante menstruationem (before menstruation); (3) ante mortem (before death)
AMA	American Medical Association
AMAPI	Association of Medical Advisers in the Pharmaceutical Industry (UK)
AMC	Academic Medical Center
AMG	Arzneimittelgesetz (Medicines Act, Austria, Germany)
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (new healthcare bill requesting an added benefit for drugs; Germany)
AMI	Acute Myocardial Infarction
AMIP	Association des Médecins de l'Industrie Pharmaceutique
AML	Acute Myelogenous Leukaemia
AMM	Authorisation de Mise sur le Marché
AMS	Accelerator Mass Spectrometry
ANCOVA	Analysis of Co-Variance (covariate adjustment)
ANDA	Abbreviated New Drug Application
ANF	Antinuclear Factor
ANOVA	Analysis of Variance
ANSM	Agence Nationale de Sécurité du Médicament (former AFSSAPS)
AOA	American Osteophathic Association
AOD	Arterial Occlusive Disease
APA	American Psychiatric Association
APACHE	Acute Physiology and Chronic Health Evaluation
APhA	American Pharmaceutical Association
API	Active Pharmaceutical Ingredient (EC)
APMA	Australian Pharmaceutical Manufacturers Association
API	Active Pharmaceutical Ingredient
APPA	Australian Pharmaceutical Physicians Association
APUA	Alliance for the Prudent Use of Antibiotics
AQL	Acceptable Quality Level
AR	(1) Airway Resistance; (2) Assessment Report (EC)
ARC	(1) AIDS Related Complex; (2) Assistant de la Recherche Clinique (syn. CRA)

ARCNO	Adverse Reaction Number (WHO Arverse Reaction Terminology)
ARDS	Adult Respiratory Distress Syndrome
ARF	(1) Acute Respiratory Failure; (2) Acute Renal Failure
ART	Adverse Reaction Terminology (WHO)
A-SAA	Acute phase Serum Amyloid A
ASA	(1) Acetyl Salicylic Acid; (2) Adam Stokes Attack; (3) American Society of Anesthesiologists
ASC	(1) Altered State of Consciousness; (2) Adult Stem Cell
ASCII	American Standard Code for Information Interchange
ASCO	American Society of Clinical Oncology
ASI	Anxiety Status Inventory
ASMF	Active Substance Master File
ASR	Annual Safety Report
AS-ODN	Antisense-Oligodeoxynucleotide
ATC	(1) Anatomical Therapeutic Chemical Classification System (WHO); (2) Animal Test Certificate
ATCC	American Type Culture Collection
ATMP	Advanced Therapy Medicinal Product (EC)
AUC	Area Under(concentration/time) the Curve
AV	(1) Atrio-Ventricular; (2) Audio-Visual
AWP	Average Wholesale Price

BA	(1) Bachelor of Arts; (2) Biological Age
BACOP	Bleomycine, Adriamycine, Cyclophosphamide, Oncovine, Prednisone
BAD	British Association of Dermatologists
BAH	Bundesverband der Arzneimittelhersteller
BAN	British Approved Names
BARDI	Bayesian Adverse Reaction Diagnostic Instrument
BARQA	British Association of Research Quality Assurance
BBB	Blood Brain Barrier
BBT	Basal Body Temperature
BC	(1) Breathing Capacity; (2) Birth Control; (3) Bone Conduction; (4) Bronchial Carcinoma; (5) Bronchite Chronique (chronic bronchitis)
BCDF	B Cell Differentiation Factor
BCG	Bacillus Calmette Guerin
BCGF	B Cell Growth Factor
BCh	Bachelor of Surgery
BCM	Birth Control Medication
Bd	Bis in Die (twice daily)
BEVAFI	Belgische Vereniging van de Artsen van de Farmaceutische Industrie (belgian society of physicians in the pharmaceutical industry)

BFID	Brancheforeningen af Farmaceutiske Industrivirksomheder i Danmark (association of pharmaceutical industries in Denmark)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Health Office, Berlin, former BGA)
BGA	Bundesgesundheitsamt (German Federal Health Office, Berlin, now BfArM)
BHF	British Heart Foundation
BI	Broca Index
BIAMP	Bundesinstitut für Arzneimittel und Medizinprodukte (former BGA, German Federal Institute for pharmaceutical and medical products)
BID	Bis In Die (two times daily)
BIRA	British Institute of Regulatory Affairs
BL	Burkitt Lymphoma
BLAs	Biologics License Applications
BLQ	Below the Limit of Quantification
BL1	Biosafety Level one
BMA	British Medical Association
BMD	Bone Mineral Density
B.Med.	Bachelor of Medicine
BMI	Body-Mass-Index
BMR	Basal Metabolic Rate
B.M.S	Bachelor of Medical Science
BMT	Bone Marrow Transplant
BN	Batch Number
BNF	British National Formulary
BNP	Brain Natriuretic Peptide
BOCF	Baseline Observation Carried Forward
BP	(1) British Pharmacopoeia; (2) Blood Pressure; (3) Birth Place
BPC	(1) British Pharmacopoeia Codex (Commission); (2) Bonnes Pratiques Cliniques (French GCP)
BPH	Benign Prostatic Hyperplasia
BPI	Bundesverband der Pharmazeutischen Industrie (Germany)
BPM	Beats Per Minute
BPRS	Brief Psychiatric Rating Scale
BPZ	Beipackzettel (package insert)
BrAPP	British Association of Pharmaceutical Physicians
BRM	Biological Response Modifyer
BS	(1) Bowel Sounds; (2) Breathing Sounds
B.S.	Bachelor of Surgery
BSE	(1) Bovine Spongioform Encephalopathy; (2) Breast Self Examination
BSI	British Standards Institution
BSRS	Behavior and Symptom Rating Scale
BT	Bleeding Time
BW	Body Weight

CA	(1) Carcinoma; (2) Confidentiality Agreement; (3) Cytosine Arabinoside; (4) Chronological Age
CABG	Coronary Artery Bypass Graft
CAD	(1) Computer Aided Design; (2) Coronary Artery Disease
CADD	Computer Assisted Drug Design
CADRIS	Canadian Adverse Drug Reaction Information System
CAFVP	Cyclophosphamide, Adriamycine, 5-Fluorouracil, Vincristine, Prednisone
CAG	(1) Coronary Angiography; (2) Carotid Angiogram
CAHD	Coronary Atherosclerotic Heart Disease
CALS	(1) Cyclophosphamide, Adriamycine, Methotrexate, Procarbacine; (2) Computer-aided Acquisition and Logistic Support
CAMA	(1) Computer Assisted Marketing Authorisation application (Europe); (2) Computer Assisted Marketing Application (US)
CANC	Cancellation (FDA: inspection not conducted)
CANDA	Computer Assisted New Drug Application (US)
CANDS	Computer Assisted New Drug Submission (Canada)
CAO	Coronary Artery Occlusion
CAOS	Cosmogen (Actinomycine D), Adriamycine (Doxorubicine), Oncovine (Vincristine), Sendoxane (= Endoxan + Cyclophosphamide)
CAP	(1) Centrally Authorised Product (EMA); (2) Coordinated Assessment Procedure (EMA)
CAPA	Corrective And Preventive Action (FDA)
CAPLA	Computer Assisted Product Licence Application
CAPLAR	Computer Assisted Product Licensing Application Review (US)
CAS	(1) Chemical Abstract Service; (2) Chemical Abstract Substance
CB	Cannabinoid Receptor
CBA	Cost Benefit Analysis
CBC	Complete Blood Count
CBCD	Chronic Bullous Disease of Childhood (IgA linear dermatosis)
CBD	(1) Chemical and Biological Description (EMA); (2) Cannabidiol
CBER	Center for Biologics Evaluation and Research (US)
CBF	(1) Cerebral Blood Flow; (2) Coronary Blood Flow
CBS	Chronic Brain Syndrome
CBI	Confederation of British Industry
CC	(1) Cervical Carcinoma; (2) Chief Complaint; (3) Coefficient of Correlation; (4) Common Cold; (5) Critical Condition; (6) Current Complaints
CCC	Copyright Clearance Centre
CCDS	Company Core Data Sheet

CCF	Congestive Cardiac Failure
CCI	Collateral Circulation Index
CCID	Cell Culture Infectious Dose
CCL	Centrocystic Lymphoma
CCM	(1) Congestive Cardiomyopathy; (2) Commission Consultative Médicale (France)
CCr	Creatinine Clearance
CCSI	Company Core Safety Information
CCNU	Methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
CCPPRB	Comités Consultatifs de Protection des Personnes dans la Recherche Biomédicale (french ethics committee)
CCRC	Certified Clinical Research Coordinator
CCT	(1) Controlled Clinical Trial; (2) Compressed Coated Tablet
CCU	Coronary Care Unit
CD	(1) Cardiovascular Disease; (2) Cardiac Diameter; (3) Celiac Disease; (4) Coma Diabétique; (5) Cesarian Delivered; (6) Contact Dermatitis; (7) Contagious Disease; (8) Curative Dose
CDA	Confidential Disclosure Agreement
CDC	(1) Center for Disease Control (US); (2) Calculated Date of Confinement
CDER	Center for Drug Evaluation and Research (US)
CDISC	Clinical Data Interchange Standards Consortium
CDM	Clinical Data Management
CDP	Clinical Development Plan
CDRH	Center for Devices and Radiological Health (US)
CD-ROM	Compact Disc – Read-Only Memory
CDS	Chemical Delivery System
CDSM	Committee on Dental and Surgical Materials (UK)
CD-WORM	Compact Disc – Write Once, Read Many
CE	(1) Concomitant Event; (2) Clinical Event; (3) Cardiac Enlargement
CEA	(1) Cost Effectiveness Analysis; (2) Carcino-Embryonic Antigen
CEC	Commission of the European Community
CEN	Comité Européen de Normalisation (European Committee of Normalisation/standardization)
CENELEC	Comité Européen de Normalisation Électrotechnique
CEO	Chief Executive Officer
CEP	Certificate of Suitability (EC)
CF	(1) Cystic Fibrosis; (2) Cardiac Failure
CFCs	Chloro-fluorocarbons
CFR	(1) Code of Federal Regulations (US); (2) Complement Fixation Reaction
CFU	Colony Forming Unit

CG	Control Group
CGD	Chronic Granulomatous Disease
CGI	Clinical Global Impression Scale
CGM	Computer Graphics Metafile
CGU	Chronic Gastric Ulcer
ChB	Batchelor of Surgery
CHD	(1) Coronary Heart Disease; (2) Chediak Higashi Disease; (3) Childhood Disease
CHF	Congestive Heart Failure
CHMP	Committee for Human Medicinal Products
CHO	Chinese Hamster Ovary
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CI	(1) Cardiac Index; (2) Capacité Inspiratoire; (3) Cardiac Infarction; (4) Coronary Insufficiency; (5) Contre Indication
CIB	Clinical Investigators' Brochure
CIM	Computer-Integrated Manufacturing
CIOMS	Council for International Organisation of Medical Sciences
CIS	(1) Commonwealth of Independent States; (2) Carcinoma In Situ; (3) Chemical Information System
CJD	Creutzfeldt Jakob Disease
CL	(1) Compulsory Licensing; (2) Clearance
CLL	Chronic Lymphatic Leukaemia
CM	Causa Mortis (reason of death)
CMA	Cost Minimisation Analysis
Cmax	Maximum Drug Concentration
CM&C	Chemical, Manufacture & Control
CMC	Chemistry, Manufactur4ing and Controls
CME	Continued Medical Education
CMFP	Cyclophosphamide, Methotrexate, 5-Fluorouracile, Prednisone
CMFV	Cyclophosphamide, Methotrexate, 5-Fluorouracile, Vincristine
CMFVP	Cyclophosphamide, Methotrexate, 5-Fluorouracile, Vincristine, Prednisone
CMI	Concentration Minimale Inhibitrice
CML	Chronic Myelogenous Leukaemia
CMO	(1) Chief Medical Officer; (2) Contract Manufacturing Organisation
CMR	Client Meeting Report
CMS	Concerned Member State (EC)
CMV	(1) Cytomegalovirus; (2) Controlled Mechanical Ventilation
CNAMTS	(French Health Insurance Agency)
CNIL	Commission Nationale de l'Informatique et des Libertés (French commission to which each clinical study, including full

	details concerning trialist, number of patients a.s.o., has to be notified)
CNOM	Conseil National de l'Ordre des Médecins (France)
CO	(1) Cardiac Output; (2) Carbon Monoxide; (3) Contractual Obligations; (4) Change Order; (5) Complains Of; (6) Compliance Officer
COA	Condition On Admission
COAD	Chronic Obstructive Airway Disease
COBOL	Common Business Oriented Language
COC	Combined Oral Contraceptives
COCIR	Coordination Committee of the Radiological and Electromedical Industries
COLD	Chronic Obstructive Lung Disease
COMPASS	Computerised On-line Medicaid Pharmaceutical Analysis and Surveillance System
CONSORT	Consolidated Standards for Reporting Trials
COO	Chief Operating Officer
COPD	Chronic Obstructive Pulmonary Disease
COPP	Cyclophosphamide, Vincristine, Procarbazine, Prednisone
COPS	Cost of Producing Sales
COSTART	Codification of Standard Terminology for Adverse Reaction Terms, Coding System for a Thesaurus of Adverse Reaction Terms
COTS	Commercial Off-The-Shelf
COX-2	Cyclooxygenase-2
CP	(1) Centralised Procedure; (2) Cor Pulmonale, coeur pulmonaire
CPA	(1) Commonwealth Pharmaceutical Association (2) Clinical Pathology Accreditation
CPI	Consumer Price Index
CPM	Critical Path Method
CPMP	Committee for Proprietary Medicinal Products
CPR	Cardio Pulmonary Resusication
CR	(1) Clinical Records; (2) Complete Response; (3) Controlled Release
CRA	Clinical Research Associate, Clinical Research Assistant
CRC	Clinical Research Coordinator
CRD	(1) Chronic Renal Disease; (2) Chronic Respiratory Disease
CRE	Clinical Research Executive
CREST	Scientific and Technical Research Committee
CRF	(1) Case Record Form, Case Report Form, Clinical Record Form; (2) Corticotropin-Releasing Factor
CRIOC	Consumer Organisations Research and Information Centre (Brussels)
CRLs	Complete Response Letters (FDA)

CRM	(1) Clinical Research Manager; (2) Committee on the Review of Medicines (UK advisory committee)
CRO	Contract Research Organisation
CRP	C-reactive Protein
CRU	Clinical Research Unit
CS	(1) Clinical Staging; (2) Complete Stroke
CSA	Clinical Study Authorisation
CSD	Committee on Safety of Drugs ("Dunlop Committee", UK)
CSM	Committee on Safety of Medicines (UK)
CSR	Clinical Study Report
CSP	Core Safety Profile
CT	(1) Clinical Trial; (2) Computer Tomography
CTA	Clinical Trial Authorisation
CTC	(1) Common Toxicity Criteria; (2) Clinical Trial Certificate
CTD	Common Technical Document document used to apply for marketing authorisation
CTE	Clinical Trial Exemption
CTFA	Cosmetic, Toiletry and Fragrance Association
CTN	Clinical Trial Notification
CTR	(1) Clinical Trial Register (EU); (2) Clinical Trial Report
CTS	(1) Clinical Trial Supplies; (2) Common Type System (Microsoft.NET)
CTX	Clinical Trial Exemption (UK)
CUA	Cost Utility Analysis
CUP	Carcinoma of Unknown Primary
CV	(1) Coefficient of Variation; (2) Curriculum Vitae; (3) Cardio Vascular
CVA	(1) Cerebro Vascular Accident; (2) Cardio Vascular Accident
CVD	(1) Cardiovascular Disease; (2) Cerebrovascular Disease
CVMP	Committee for Veterinary Medicinal Products
CVPP	Cyclophosphamide, Vinblastine, Procarbazine, Prednisone
CXR	Chest X Ray
CYP	Cytochrome P450

DA	(1) Data Audit (FDA); (2) Delayed Action (of a drug); (3) Drug Abuser
DAD	Dispense as Directed
DAMOS	Dokumentation zu Arzneimitteln auf optischen Speichern (Germany)
DASS	Dezentrales Auftrags-Steuerungs System
DB	Double Blind
DBP	Diastolic Blood Pressure
DBT	Double Blind Trial
DC	Death Certificate

D&C	(1) Dilation and Curettage; (2) Drugs and Cosmetics
DCF	Data Collection Form
DCH	Delayed Cutaneous Hypersensitivity
D.Ch.	Doctor Chirurgiae
DCP.	Decentralised Procedure
DCS.	Deliverable Class Standard
DDA	Dangerous Drug Act (US)
DDD	Defined Daily Dose
DDG	Degenerative Disc Disease
DDH	Delayed Dermal Hypersensitivity
DDL	Dear Doctor Letter
DDPS	Detailed Description of the Pharmacovigilance System (obsolete term)
DDX	Doctor's and Dentist's Exemption scheme (from the need to obtain formal approval to do clinical trials in the UK)
DEC	Drug Event Combination
DESI	Drug Efficacy Study Implementation (FDA program)
DEA	Drug Enforcement Agency (US)
DFI	Disease Free Interval
DFS	Disease Free Survival
DG	(1) Director General; (2) Drafting Group (EMA)
DGPharMed	Deutsche Gesellschaft für Pharmazeutische Medizin (former FÄPI)
DGSF	(Italian Drugs Directorate)
DHHS	Department of Health and Human Services (US)
DHPC	Direct Healthcare Professional Communication (EU)
DHT	Delayed Type Hypersensitivity
DIA	Drug Information Association
DIBD	Development International Birth Date (EMA)
DIC	Disseminated Intravascular Coagulation
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DIN	Deutsche Industrie-Norm (Deutsches Institut für Normung e.V.)
DIPS	Drug Interaction Probability Scale
DISC	Disabled Infectious Single Cycle Viral Vector
DJD	Degenerative Joint Disease
DLP	Data Lock-Point
DM	Disease Management
DMAC	Division of Drug Marketing, Advertising and Communications (FDA)
DMARD	Disease Modifying Antirheumatic Drug

DMC	(1) Drug Monitoring Committee (2) Data Monitoring Committee
DMD	(1) Disease Modifying Drug; (2) Duchenne Muscular Dystrophy
DME	Drug Metabolism Enzyme
DMF	Drug Master File
DMOS	Diverses Mesures d'Ordre Social (French law concerning financial benefits of physicians offered by the pharmaceutical industry)
DOB	Date of Birth
DoH	Department of Health (UK)
D.P.	Doctor of Pharmacy
DPM	Diploma in Psychological Medicine
DRF	Data Resolution Form
DRL	Drug Reference List (WHO)
DSD	Drug Surveillance Departement
DSM	(1) Drug Safety Monitoring; (2) Diagnostic and Statistical Manual of Mental Disorders (of the American Psychiatric Association)
DSMB	Drug and Safety Monitoring Board
DSRU	Drug Safety Research Unit (UK)
DSUR	Development Safety Update Report (EMA)
DTC	Direct-To-Consumer
DTD	Document Type Definition
DTP	(1) Diphtheria-Tetanus-Poliomyelitis; (2) Desk Top Publishing
DU	Duodenal Ulcer
DUR	Drug Utilisation Review
DUS	Drug Utilisation Study
DVT	Deep Vein Thrombosis
e	(as prefix) electronic
EAACI	European Academy of Allergology and Clinical Immunology
EAE	Experimental Allergic Encephalitis, Experimental Autoimmune-Encephalitis
EAEMP	European Agency for the Evaluation of Medicinal Products
EAN	European Article Numbering
EANM	European Association of Producers and Distributors of Natural Medicines
EBC	European Business Council
EBGM	Empirical Bayes Geometric Mean
EBM	Evidence Based Medicine
EBV	Eppstein Barr Virus
EC	(1) Ethics Committee; (2) European Community; (3) European Commission
eCB	endocannabinoid system

ECDD	Expert Committee on Drug Dependence (WHO)
ECE	Endothelin Conversion Enzyme
ECG	Electrocardiogram
ECHO	Enteric Cytopathogenic Human Orphan (virus)
ECITC	European Committee or European Commission
ECJ	European Court of Justice
ECOG	Eastern Cooperative Oncology Group
ECT	Enteric Coated Tablet
ECU	European Currency Unit
ED50	Median Effective Dose
EDC	Electronic Data Capture
EDI	Electronic Data Interchange
EDL	Essential Drug List
EDMA	European Diagnostic Manufacturers Association
EDMF	European Drug Master File
EDMUS	European Database on Multiple Sclerosis
EDP	Electronic Data Processing
EDQM	European Directorate for the Quality of Medicines
EDV	End Diastolic Volume
EEA	European Economic Area
EEC	European Economic Community
EEG	Electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic Medicines Association
EHR	Electronic Healthcare Record
EIR	Establishment Inspection Report
EINECS	European Inventory of Existing Commercial Chemical Substances
EFPIA	European Federation of Pharmaceutical Industries Associations (Brussels)
EFSA	European Food Safety Authority
EFTA	European Free Trade Association
EGA	European Generic medicines Association
EGF	Epidermal Growth Factor
EIA	Exercise Induced Asthma
EINECS	European Inventory of Existing Commercial Chemical Substances
EIRnv	Extra Incidence Rate in non-vaccinated groups
EIRv	Extra Incidence Rate in vaccinated groups
EKG	Electrocardiogram
ELA	Establishment License Application
ELISA	Enzyme Linked Immunosorbent Assay
E of M	Error of Measurement
EMA	European Medicines Agency (former EMEA)
EMEA	European Agency for the Evaluation of Medical Products (the European Union's regulatory agency, now EMA)
EMG	Electromyelogram

EN	European Norm
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOQ	European Organization for Quality
EORTC	European Organization for Research and Treatment of Cancer
EOTC	European Organization for Testing and Certification
EP	(1) European Pharmacopoeia; (2) European Parlament
EPA	Environmental Protection Agency (US)
EPAR	European Public Assessment Report
EPC	(1) European Patent Convention; (2) European Pharmacopoeial Convention
EPD	Electronic Patient Diaries
EPhMRA	European Pharmaceutical Market Research Association
EPLC	European Pharma Law Centre (Surrey, UK; e.g., EC document database)
ePRO	electronic Patient-Reported Outcomes
EPS	Earnings Per Share
ER	Extended-Release
ERA	Environmental Risk Assessment
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
ESC	Embryonic Stem Cell
ESCOP	European Scientific Corporation of Phytotherapy
ESCP	European Society of Clinical Pharmacy
ESF	European Science Foundation
ESO	European School of Oncology
ESOP	European Society of Pharmacovigilance
ESP	Extrasensory Perception
ESR	Erythrocyte Sedimentation Rate
ESRA	European Society of Regulatory Affairs
et al.	et alii (and coworkers)
ETSI	European Telecommunication Standard Institute
EU	European Union
EUCOMED	European Confederation of Medical Device Associations
Eudamed	European Database for Medical Devices
EudraCT	European Clinical Trials Database
EudraVigilance	**E**uropean **U**nion **D**rug **R**egulating **A**uthorities Pharmaco**vigilance**
EUFEPS	European Federation of Pharmaceutical Sciences
EUROM VI	European Federation of Precision, Mechanical and Optical Industries
EUROPAM	European Herb Growers Association
EVA	Echelle Visuelle Analogique (visuel analogue scale)

EVDAS	EudraVigilance Data Warehouse and Analysis System (EMAs searchable database for ICSRs)
EVIMPD	EudraVigilance Investigational Medicinal Product Dictionary
EVMPD	EudraVigilance Medicinal Product Dictionary (EMAs searchable database for authorised medicinal products, APIs and ingredients)
EVPM	EudraVigilance Post-authorisation Module (EMAs database for ICSRs of all authorised medicinal products)
EVPRM	EudraVigilance Product Report Message
EWL	Evaporated Water Loss
EXP	Expiry Date
F1	Offspring from first generation
FÄPI	Fachgesellschaft der Ärzte in der Pharmazeutischen Industrie (now DGPharMed, German society of physicians in the pharmaceutical industry)
FBC	Full Blood Count
FC	For Cause inspection (FDA)
FCA	Freund's Complete Adjuvant
FDA	(1) Food and Drug Administration (US); (2) Federal Drug Agency (US)
FD&C	Food, Drugs and Cosmetics (US)
FDD	Functional Digestive Disorders
FELASA	Federation of European Laboratory Animal Science Associations
FERQAS	Federation of European Research Quality Assurance Societies
FEFIM	Fédération Française des Industries du Médicament
FFPM	Fellow of the Faculty of Pharmaceutical Medicine (UK)
FI	Fachinformation (German international physician's circular)
FIA	Landelijke Vereniging van Farmaceutische Industrie-Artsen (Dutch association of physicians in the therapeutical industry)
FIH	First-in-Human
FIP	Fédération Internationale Pharmaceutique (International Pharmaceutical Federation)
FLE	Foreningen af Laeger i Erhvervslivet (Danish assocation of physicians in private employment)
FMP	First Menstrual Period
FOI	Freedom of Information (US)
FORTRAN	Formula Translation
FP	Family Practitioner
FPI	First Patient In
FPIF	Finnish Pharmaceutical Industry Federation

FPO	First Patient Out
FRAM	Fund for the Replacement of Animals in Medical Research
FRCGP	Fellow of the Royal College of General Practitioners
FRCP	Fellow of the Royal College of Physicians
FSC	Free Sales Certificate
FTC	Free Trade Commission (US)
5-FU	5-fluorouracil
FUO	Fever of Unknown (Undetermined) Origin
FYI	For Your Information

GALP	Good Automated Laboratory Practice
GALM	Good Automated Manufactoring Practice
GAO	General Accounting Office (US)
GAR	Grant Appropriation Request
GATT	General Agreement on Tariffs and Trade
GCP	Good Clinical Practice
GCRP	(1) Good Clinical Research Practice; (2) Good Clinical Regulatory Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GCTP	Good Clinical Trial Practice
GDP	(1) Gross Domestic Product; (2) Good Distribution Practice
GERD	Gastro-Oesophageal Reflux Disease
GFR	Glomerular Filtration Rate
GH	Growth Hormone
GHTF	Global Harmonization Task Force
GI	(1) Gastro-Intestinal; (2) Gingival Index
GILSP	Good Industrial Large Scale Practice
GIT	Gastro-Intestinal Tract
GLC	Gas Liquid Chromatography
GM	General Medicine
GMC	General Medical Council
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMM	Genetically Modified Microorganism
GMDN	Global Medical Device Nomenclature
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GNP	Gross National Product
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
GPCRs	G-Protein Coupled Receptors
GPDR	General Practice Research Database (UK; formerly VAMP)
GPIA	Generic Pharmaceutical Industry Association
GPM	(1) Gesellschaft für Pharmazeutische Medizin (Austria); (2) German Project Management Association

GPMSP	Good Postmarketing Surveillance Practice (Japan)
GPS	Good Pasture Syndrom
GPvP	Good Pharmacovigilance Practice (also GVP)
GRAS	Generally Recognised as Safe
GRG	Gesundheits-Reform-Gesetz (Germany)
GRP	Good Regulatory Practice
GSG	Gesundheit-Struktur-Gesetz (Germany)
GSL	General Sale List medicine (UK)
GSP	Good Storage Practice
GTT	Glucose Tolerance Test
GU	Gastric Ulcer
GVHD	Graft Versus Host Disease
GVP	(Guideline on) Good Pharmacovigilance Practice (also GPvP)
GxP	Good Practice (of any activity)

H0	Null Hypothesis
H1	Alternative Hypothesis
HA	Hepatitis A Haemophilia A
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Rating Scale
HAV	Hepatitis A Virus
HB	Hepatitis B
HBV	Hepatitis B Virus
HC	Hepatitis C
HCFA	Health Care Fiancing Administration (US)
HCL	Hairy Cell Leukemia
HCMV	Human Cytomegalovirus
HCV	Hepatitis C Virus
HDP	Hypertensive Disease in Pregnancy
HDRS	Hamilton Depression Rating Scale
hESCs	human Embryonic Stem Cells
HHV	Human Herpes Virus
HIMA	(1) Health Industry Manufacturers Association (US); (2) Heads of Medicines Agencies (EU)
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
HLGT	High Level Group Term (MedDRA)
HLT	High Level Term (MedDRA)
HMA	(1) Host Mediated Assay; (2) Heads of Medicines Agencies (EU)
HMO	Health Maintenance Organisation (US)
HME	Hot-Melt Extrusion
HNANB	Hepatitis non A non B
HO	(1) Heterotrophic Ossification; (2) House Officer, junior hospital doctor

HPI	History of Present Illness
HPLC	High Performance Liquid Chromatography
HPRSD	Hamilton Psychiatric Rating Scale for Depression
HPV	Human Papilloma Virus
HR	Heart Rate
HRQOL	Health Related Quality Of Life
HRS	Herpes Simplex Encephalitis
HRT	Hormone Replacement Therapy
HSA	Health Science Authority (US)
hSC	human Stem Cell
HSV	Herpes Simplex Virus
HT	High level Term
HTA	Health Technology Assessment
HUGO	Human Genom Organization
HYE	Healthy Year Equivalent
HZV	Herpes Zoster Virus

IABS	International Association of Biological Standardisation
IAPM	International Association of Medical Prosthesis Manufacturers
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
IBD	(1) Inflammatory Bowel Disease; (2) International Birth Date
IBS	Irritable Bowel Syndrome
IBW	Ideal Body Weight
IC	Inhibitory Concentration
ICAT	International Comprehensive Anatomical Terminology
ICD	Intrauterine Contraceptive Device (= IUD)
ICD-9	International Classification of Diseases, 9th edition
ICD-10	International Classification of Diseases, 10th edition (1992)
ICDA	International Classification of Disease Adapted
ICD-O	International Classification of Diseases for Oncology (WHO)
ICE	Innovative Chemical Extension
ICF	Informed Consent Form
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICH	International Conference on Harmonisation (EC)
ICIDH	International Classification of Impairments, Disabilities, and Handicaps (WHO)
ICPC	International Classification of Primary Care (ICPC-2)
ICTRP	International Clinical Trials Registry Platform (WHO)
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IDB	Investigator's Drug Brochure
IDCT	Investigator Driven Clinical Trial
IDD	Immunodeficency Disease

IDDM	Insulin-Dependent Diabetes Mellitus
IDE	Investigational Device Exemption
IDLH	Immediately Dangerous to Life or Health (gas-concentrations)
IDMP	Identification of Medicinal Products (standards, ISO)
i.e.	id est (namely)
IEC	Independent Ethics Committee
IEEE	Institute of Electrical and Electronic Engineers (US)
IFAPP	International Federation of Associations of Pharmaceutical Physicians
IFDES	International Foundation for Drug Efficacy and Safety
IFN	Interferon
IFPMA	International Federation of Pharmaceutical Manufacturers' Associations
IFPP	International Federation of Pharmaceutical Physicians
IGES	Initial Graphics Exchange Standard
IH	Infectious Hepatitis
IHD	Ischaemic Heart Disease
IIT	Investigator Initiated Trial
IKS	Interkantonale Kontrollstelle für Heilmittel
ILS	Increase in mean/median Life Span
IME	Inborn Metabolic Error
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMRAD	Introduction, Material/Methods, Results, Discussion
IMRBF	International Medical Risk Benefit Foundation
IND	(1) Investigational New Drug; (2) Innovative New Drug
INN	International Non-Proprietary Name
INTDIS	International Drug Information System
IOCU	International Organisation of Consumers Unions
IOP	Increase in intraocular Pressure
IP	Intellectual Property
IPAC	International Pharmaceutical Aerosol Consortium
IPEC	International Pharmaceutical Excipients Council
IPH	International Pharmacopoeia
IPMRG	International Pharmaceutical Market Research Group
IPO	Initial Public Offering
IPRG	Interdisciplinary Pharmacogenomics Review Group
iPSC	induced Pluripotent Stem Cell
IPTSB	International Programs and Technical Support Branch (FDA office for inspections)
IQ	Installation Qualification (of software)
IRB	Institutional Review Board
IRDS	Infant Respiratory Distress Syndrome
IS	Infarct Size
ISBN	International Standard Book Numbering
ISO	International Organization for Standardization

ISPOR	International Society for Pharmacoeconomics and Outcome Research
ISRCTN	International Standard Randomised Controlled Trial Number
ISS	(1) Installation Support Services; (2) Integrated System Support
IT	Information Technology
ITC	Indirect Treatment Comparison
ITP	Immune Thrombocytopenic Purpura
ITQS	Information Technology Quality System
ITT	Intent-To-Treat
IU	International Unit
IUCD	Intra-Uterine Contraceptive Device
IUD	Intra-Uterine Device
IUPAC	International Union of Pure and Applied Chemistry
IVD	(1) In-Vitro Diagnostic; (2) In-Vitro Device
IVP	Intravenous Pyelography
IVRS	Interactive (or Integrated) Voice Response System
IWRS	Interactive Web Response System
JPMA	Japanese Pharmaceutical Manufacturers Association
JRA	Juvenile Rheumatoid Arthritis
KOL	Key Opinion Leader
LA	Licensing Authority
LAF	Lymphocyte Activating Factor
LAg1	Longevity Assurance Gene
LAL	Limulus Amebocyte Lysate Test
LAN	Local Area Network
LASA	Linear Analogue Self Assessment
LD	Lethal Dose
LDLo	Lowest Lethal Dose
LFT	Liver Function Test
LHA	Local Health Authority
LLOQ	Lower Limit Of Quantification
LMWH	Low Molecular Weight Heparin
LNT	Linear No Threshold
LOCF	Last Observation Carried Forward
LPI	Last Patient In
LPO	Last Patient Out
LREC	Local Research Ethics Committee
LRTI	Lower Respiratory Tract Infection
LUTI	Lower Urinary Tract Infection
LUTS	Lower Urinary Tract Symptoms
LVCF	Last Visit Carried Forward, Last Value Carried Forward

LVF	Left Ventricular Failure
LVH	Left Ventricular Hypertrophy
MA	(1) Marketing Authorisation; (2) Master of Arts
MAA	(1) Marketing Authorisation Application; (2) Marketing Approval Authorisation
MAb or mAB	Monoclonal Antibody
MABEL	Minimum Anticipated Biological Effect Level
MADRS	Montgomery–Asberg Depression Rating Scale
MAFS	Mezinarodni Asociace Farmaceutickych Spolecnosti (Czech Association of Research Based Pharmaceutical Companies)
MAH	Marketing Authorisation Holder
MAL	Maximum Admissible/Allowed Limit
MaLAM	Medical Lobby for Appropriate Marketing
MANOVA	Multivariate Analysis of Variance
MAP	Mean Arterial Blood Pressure
MB	(1) Bachelor of Medicine; (2) Mängelbericht (report of the German BGA concerning deficiencies of a new drug application)
MBD	Metastatic Bone Disease
MBO	Management Buy-Out
MCA	Medicines Control Agency (UK)
MCD	Multiple Carboxylase Deficiency
MCID	Minimal Clinically Important Difference
MCT	Multi-Centre Trial
MCO	Managed Care Organisation
MD	(1) Maximum Acceptable Difference; (2) Medical Doctor
MDD	(1) Medical Devices and Diagnostics; (2) Medical Device Directive
MDEG	Medical Device Expert Group (EC)
MDI	Metered Dose Inhaler
MDR	Multi-Drug Resistance
MEC	Minimum Effective Concentration
MED	Minimum Effective Dosage
MEDDRA	Medical Dictionary for Drug Regulatory Activity
MEDIF	(Pharmaceutical industries association in Denmark)
MEDLARS	Medical Literature Analysis and Retrieval System (of the National Library of Medicine, Bethesda, Md., US)
MEDORA	Medical Dictionary for Drug Regulatory Affairs
MEFA	(Danish domestic pharmaceutical industry association)
MEMS	Medication Event Monitoring System
MeSH	Medical Subject Heading
MFPM	Member of the Faculty of Pharmaceutical Medicine (UK)
MHRA	Medicines and Healthcare products Regulatory Agency (UK; previous: MCA)

MI	(1) Medicines Inspectorate (UK); (2) Myocardial Infarction; (3) Mitotic Index
MIC	Minimal Inhibitory Concentration
MID	Minimal Infective Dose
MIF	Migration Inhibition Factor
MIMS	Monthly Index of Medical Specialities
miRNA	micro RNA
MIS	Management Information System
ML	Maximum Limit
MLD	Minimum Lethal Dose
MMR	Measles/Mumps/Rubella
MMRM	Mixed Models Repeated Measures
MNC	Multi-National Company
MNLD	Maximum Non-Lethal Dose
MODEM	MOdulator/DEModulator
MODS	Multi-Organ Dysfunction Syndrome
MOS	Medical Outcome Study (quality of life instrument)
MOU	Memorandum Of Understanding (US)
MPD	Maximal Permissible Dose
MR	Medical Representative
MRC	Medical Research Council (UK)
MRCP	Magnetic Resonance Cholangio-Pancreatography
MRD	Maximum Repeatable Dose
MRFG	Mutual Recognition Facilitation Group
MRL	Maximum Residue Limit
MRP	Mutual Recognition Procedure (EMA)
MRSD	Maximum Recommended Starting Dose
MRT	Multiple Sclerosis
MS	Mass Spectrometry
MS	Mean Residence Time
MSA	Multi State Application
MSF	Médecins Sans Frontières
MTC	Minimum Toxic Concentration
MTD	(1) Maximal Tolerated Dose; (2) Minimal Toxic Dose
MTR	Monitor's Trip Report
MU	Million Units
MULT	Mucosa-Associated Lymphoid Tissue
MW	Molecular Weight

NA	Not Applicable
NACDS	National Association of Chain Drug Stores (US)
NAD	No Abnormality Detected
NADA	New Animal Drug Application
NAF	Notification of Adverse Findings (US)

NAFTA	North American Free Trade Agreement
NAI	No Action Indicated (FDA)
NANDO	New Approach Notified and Designated Organisations information system (EU, devices)
NAPM	National Association of Pharmaceutical Manufacturers (US)
NAS	New Active Substance
NB	Notified Body (EU)
NBAS	New Biological Active Substance
NC	No Change
NCA	National Competent Authority (EU)
NCC	National Computing Centre (UK)
NCD	Non-Communicable Disease
NCE	New Chemical Entity
NCI	National Cancer Institute (US)
NCR	No Carbon Required paper
NCTC	National Collection of Type Cultures (London)
ND	(1) Not Done, (2) Nil Detected
NDA	New Drug Application
NDDP	New Drug Development Plan
NEC	Not Elsewhere Classified (MedDRA)
NF	Nationary Formulary (USA)
NfG	Note for Guidance (EC)
NGF	Neurotrophic Growth Factor, Nerve Growth Factor
NGO	Non-Governmental Organisation
NHS	National Health Service (UK)
NIAID	National Institute of Allergy and Infectious Diseases (US)
NICE	National Institute for Health and Clinical Excellence (UK)
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NIDPOE	Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (FDA)
NIGMS	National Institute of General Medical Sciences (US)
NIH	National Institutes of Health (US)
NIMP	Non-Investigational Medicinal Product
NLN	(Nordic Council on Medicines)
NLR	Normal Laboratory Range
NME	New Molecular Entity
NMR	Nuclear Magnetic Resonance
NMS	Neuroleptic Malignant Syndrome
NMSP	New Mathematical Statistical Package
NNT	Number Needed to Treat
NOAEL	No-Observed Adverse Event Level
NOEL	No-Effect Level
NPS	Numerical Pain Scale
NRG	Name Review Group (EMA)
nsAE	non-serious Adverse Event
NSAID	Non-Steroidal Antiinflammatory Drug

NSR	Non Significant Risk
NTA	Notice to Applicants (EC)
NTR	Narrow therapeutic range
NUG	Necrotizing Ulcerative Gingivitis
NUI	Non Urgent Information (EU)
NYHA	New York Heart Association (scale of heart failure severity)

OA	Osteoarthritis
OAI	Official Action Indicated (FDA)
OAIC	Official Action taken and/ or case Closed (FDA)
OB	Ohne Befund (no abnormality detected)
OC	Oral Contraceptive
OCD	Obsessive-Compulsive Disorder
OCR	Optical Character Recognition
OD	(1) Once Daily; (2) Overdose; (3) Oculus Dextra (right eye)
ODE	Office of Drug Evaluation (US)
ODT	Orally Disintegrating Tablet
OECD	Organisation for Economic Cooperation and Development
OHE	Office of Health Economics (UK)
OHS	Occupational Health & Safety
OMB	Office of Management and Budget
OMR	Optical Mark Recognition
OOS	Out-Of-Specification (FDA; test results for pharmaceutical production)
OPC	One-Point-Cut (ampoules)
OPRR	Office for Protection from Research Risks (US)
OQ	Operation Qualification (of software)
OR	Outcomes Research
OS	Oculus Sinistra (left eye)
OSHA	Occupational Safety and Health Administration (US)
OTA	Office of Technology Assessment (US)
OTC	Over-The-Counter
OU	Oculus Uterque (both eyes)

P	Pharmacy Only
pa	Per annum
PACT	Prescribing Analysis and Cost Data
PAES	Post-Authorisation Efficacy Study
PAF	Platelet Aggregating Factor
PAN	Pesticide Action Network
PAOD	Peripheral Arterial Occlusive Disease
PAR	(1) Post-Approval Research; (2) Public Assessment Report (EU)

PASS	Post-Authorisation Safety Study
PBM	Pharmacy (Pharmaceutical) Benefit Management, Pharmacy (Pharmaceutical) Benefit Manager
PBO	Placebo
PBRER	Periodic Benefit Risk Evaluation Report (EC)
PC	Post cibum (after meals)
PCA	Patient Controlled Analgesia
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PCSO	Pharmaceutical Contract Support Organization
PD	Progressive Disease
PDA	Parenteral Drug Association
PDCA	Plan Do Check Action-Cycle
PDCO	Paediatric Committee (EC)
PDD	Prescribed Daily Dosage
PDE	Phosphodiesterase
PDF	Portable Document Form
PDGF	Platelet Derived Growth Factor
PDR	Physicians Desk Reference
PDUFA	Prescription Drug User Fee Act (FDA)
PE	Pulmonary Embolism
PED	Pharmakoepidemiologische Datenbank (Germany)
PEF	Peak Expiratory Flow Rate
PEM	Prescription-Event Monitoring
PER	Pharmaceutical Evaluation Report
PERT	Program Evaluation Review Technique
PhD	Doctor of Philosophy
PhRMA	Pharmaceutical Research and Manufacturers of America
PhV (or PV)	Pharmacovigilance
PI	(1) Parallel Import; (2) Principle Investigator; (3) Package Insert
PIC	Pharmaceutical Inspection Convention
PICS	Pharmaceutical Inspection Cooperation Scheme
PID	Pelvic Inflammatory Disease
PIH	Pregnancy-Induced Hypertension
PIL	Patient Information Leaflet
PILS	Patient Information Leaflets
PIN	Personal Identification Number
pINN	proposed International Non-Proprietary Name
PIP	(1) Pediatric Investigational Plan; (2) Prescription Information Package; (3) Peak Inspiratory Pressure; (4) Positive Inspiratory Pressure; (5) Project Implementation Plan; (6) Process Improvement Project
PL	Product Licence, Parallel Import Product Licence

PLA	Product Licence Application (US)
PMA	(1) Pharmaceutical Manufacturers' Association; (2) Pre-Market Approval
PMAC	Pharmaceutical Manufacturers' Association of Canada
PMC	Post-Marketing Commitment
PMCF	Post Market Clinical Follow-up
PMO	Post Menopausal Osteoporosis
PMP	Proprietary Medical Product
PMS	(1) Post-Marketing Surveillance; (2) Premenstrual Stress Syndrome
PMSS	Post-Marketing Safety Study;
POM	Prescription-Only-Medication
POMS	Process Operation Management System
PPA	Prescription Pricing Authority
PPI	(1) Patient Package Insert; (2) Patient Product Information; (3) Pharmaceutical Product Information; (4) Producer Price Index
PPLO	Pleuro-Pneumonia Like Organisms
PPM	Physician Practice Management companie
PPRS	Pharmaceutical Price Regulation Scheme
PQ	Performance Qualification (of software)
PQR	Product Quality Review
PR	Partial Response
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PRISMA	Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcome
prn	pro re nata (medication to be taken as needed, at discretion of the nurse)
PSA	Prescription Sequence Analysis
PSF	Product Specification File (EC)
PSMF	Pharmacovigilance System Master File
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PT	Physical Therapy
PT	Preferred Term
PtC	Points to Consider (EU)
PTCA	Percutaneous Transluminal Coronary Angioplastie
PTO	Patent and Trade Mark Office
PTP	Previously Treated Patient
PUD	Peptic Ulcer Disease
PUO	Pyrexia of Unknown Origin
PUP	Previously Untreated Patient
PUVA	Psoralen + Ultraviolet A
PV (or PhV)	Pharmacovigilance
PVT	Paroxysmal Ventricular Tachycardia

QA	Quality Assurance
Q&A	Questions and Answers
QALY	Quality-Adjusted Life-Years
QAU	Quality Assurance Unit
QC	Quality Control
QD	Quaque Die (once daily)
qhs	quaque hora somni, i.e. “every bedtime”
QID	Quars In Die (four times daily)
QL	Quality of Life
QMS	Quality Management System
QoL	Quality of Life
QPPV	Qualified Person responsible for Pharmacovigilance (EEC)
QRD	Quality Review of Documents (EMA)
QUID	Quantitative Ingredients Declaration

r	recombinant
R	Revision
RA	(1) Rapid Alert (EU); (2) Regulatory Affairs; (3) Rheumatoid Arthritis
RAD-AR	Risk Assessment of Drugs – Analysis and Response
RAM	Random Access Memory
RAPS	Regulatory Affairs Professionals Society
RAS	Rapid Alert System
RCGP	Royal College of General Practitioners
RCC	Renal Cell Carcinoma
RCT	Randomised Controlled Clinical Trial
R&D	Research and Development
RDA	(1) Recommended Daily Allowance; (2) Recommended Dietary Allowance
RDE	Remote Data Entry
RDS	Respiratory Distress Syndrome
REM	Rapid Eye Movement
REMS	Risk Evaluation and Mitigation Strategy (FDA)
RFP	Request for Proposal
RHA	Regional Health Authority
RIA	Radioimmunoassay
RL	Richtlinie (directive)
RMP	Risk Management Plan
RMS	Reference Member State (EC)
ROC	Return On Capital
ROM	Read Only Memory
RPSGB	Royal Pharmaceutical Society of Great Britain
RR	(1) Response Rate; (2) Riva Rocci
RSI	Reference Safety Information (as in SmPC or IB)

RSM	Royal Society of Medicine
RSV	Rous Sarcoma Virus
RTECS	Registry of Toxic Effects of Chemical Substances
RTI	(1) Respiratory Tract Infection; (2) Reverse Transcriptase Inhibitor
S&A	(urine) Sugar and Acetone test
SAARD	Slow-Acting Antirheumatic Drug
SAC	(1) Standardised Assessment of Causality; (2) Safety Assessment Candidate
sAE	serious Adverse Event
SAG	Scientific Advisory Group (EMA)
SAL	Sterility Assurance Level
SAMM	Safety Assessment of Marketed Medicines
SAPS	Swedish Academy of Pharmaceutical Sciences
SAS	Statistical Analysis System
SBA	Summary Basis of Approval
SBP	Systolic Blood Pressure
SCE	Sister Chromatide Exchange
SCI	(1) Science Citation Index; (2) Spinal Cord Injury
SCS	(1) Supply Chain Solution; (2) Source Control System; (3) Special Communication System; (4) Spinal Cord Stimulation; (5) Scientific Certification System
SD	(1) Standard Deviation; (2) Stable Disease
SDA	Standardised Decision Aids
SDI	Spine Deformity Index
SDLC	Systems Development Life Cycle
SDV	Source Data Verification
SDR	Signals of Disproportionate Reporting
SEAR	Safety, Efficacy, and Adverse Reactions subcommittee (UK, advisory committee)
SEC	Securities and Exchange Commission (US)
SEM	(1) Standard Error of the Mean; (2) Scanning Electron Microscopy
SES	Summary Effect Sizes
SF 36	Short Form (36 items long) of the “Medical Outcome Study”
SG&A	Selling and General Administration
SI	Système International
SIDS	Sudden Infant Death Syndrome
SII	Science Impact Index
siRNA	small interfering RNA
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosus
SLS	Selected List Scheme

SM	Self-Medication
SMART	Submission Management and Review Tracking
SMDA	Safe Medical Devices Act
SME	Small and Medium-sized Enterprises
SMO	Site Management Organisation
SMON	Sub-Acute Myelo-Optical Neuropathy
SmPC	Summary of Product Characteristics
SNIP	Syndicat National de l'Industrie Pharmaceutique (French pharmaceutical industry association)
SNOMED	Systematized Nomenclature of Medicine
SNP	Single Nucleotide Polymorphism
SO	Safety Officer
SO	Safety Officer
SOC	System Organ Classes (MedDRA)
SOP	Standard Operating Procedures
Spa	sanitas per aquas (health through water)
SPC	(1) Summary of Product Characteristics; (2) Supplementary Protection Certificate
SPECT	Single Photon Emission Computed Tomography
SPID	Sum of Pain Intensity Differences
SPMP	Software Project Management Plan
SPR	Surface Plasmon Resonance
SPS	Summary of Pharmacovigilance System
SPSS	Statistical Package for the Social Sciences
SR	(1) Sustained Release; (2) Significant Risk
SRD	Software Requirements Document
SRS	Spontaneous Report System
SSAR	Suspected Serious Adverse Reaction
SSFA	Società di Scienze Farmacologiche Applicate (Society for Applied Pharmacological Sciences, Italian association of pharmaceutical physicians)
SSI	Structured Substance Information (EC)
SSRI	Selective Serotonine Reuptake Inhibitor
STARD	Standards for the Reporting of Diagnostic accuracy studies
STD	Sexually Transmitted Disease
STF	Study Tagging File
STM	Short Term Memory
Stp	Status post
STROBE	STrengthening the Reporting of Observational studies in Epidemiology
SUR	Safety Update Report
SUSAR	Suspected Unexpected Serious Adverse Reaction

Susp	Suspicion of
SVT	Supraventricular Tachycardia
TAA	Test Article Accountability (US)
TAP	Transporter associated with Antigen Processing
TB	Tuberculosis
TBI	Traumatic Brain Injury
TCID	Tissue Culture Infectious Dose
TdP	Torsades de Pointes
TEN	Toxic Epidermal Necrolysis
TESS	Treatment Emergent Signs and Symptoms
TCE	Time and Cost Estimate
TGA	Therapeutic Goods Administration (Australia)
TGF	Transforming Growth Factor
TIA	Transitory Ischaemic Attack
TID	Tres In Die (three times daily)
TIF	T lymphocyte-targeted Immunofusion protein
TIND	Treatment IND
TMF	Trial Master File
TMO	Trial Management Organisation
TNF	Tumor Necrosis Factor
TNM	Tumor Node Metastase (assessments in tumor patient)
TOC	Total Organ Carbon analysis
TOTPAR	Total Area under the Pain Relief curve
TPN	Total Parenteral Nutrition
TQM	Total Quality Management
TRIC	Trachoma and Inclusion Conjunctivitis
TRIPS	Trade-Related Intellectual Property (talks)
TSCA	Toxic Substance Control Act (US)
TSE	Transmissible Spongioform Encephalopathie
TTO	Time Trade-Off
TUR-P	Trans-Urethral Resection of the Prostate
UCUM	Unified Code for Units of Measure
UDI	Unique Device Identification
UDS	Unscheduled DNA repair Synthesis
UFAW	United Federation of Animal Welfare
UICC	Unio Internationalis Contra Cancrum
UGT	UDP-glucuronosyltransferase
UMDNS	Universal Medical Device Nomenclature System

UML	Unified Modeling Language
UMLS	Unified Medical Language System
UNDP	United Nations Development Programme
UNICEF	United Nations International Children's Emergency Fund
UNIDO	United Nations Industrial Development Organization
UPDRS	Unified Parkinson Disease Rating Scale
UPTD	Unit of Pulmonary Toxicity Dosage
URTI	Upper Respiratory Tract Infection
USAN	United States Adopted Names
USP	United States Pharmacopoeia
USPDI	United States Pharmacopoeia Dispensing Information
USPTO	United States Patent and Trademark Office
USR	Urgent Safety Restriction
USTR	US Trade Representative
UTI	Urinary Tract Infection
UUTI	Upper Urinary Tract Infection

VA	Veterans Administration
VAI	Voluntary Action Indicated (FDA)
VAS	Visual Analogue Scale
VAT	Value Added Tax
VD	(1) Volume of Distribution; (2) Venereal Disease
VDGS	Voluntary Genomic Data Submission
VDP	Visual Display Unit
VFA	Verband Forschender Arzneimittelhersteller (Germany)
VHP	Voluntary Harmonisation Procedure (EC)
VO	Verordnung (regulation)
VPC	Veterinary Products Committee (UK)
VT	Ventricular Tachycardia

WBS	Work Breakdown Structure
WDLL	Well Differentiated Lymphocytic Lymphoma
WFPMM	World Federation of Proprietary Medicine Manufacturers
WHO	World Health Organisation
WHO-ARD	Adverse Reaction Dictionary (WHO)
WHO-ART	Adverse Reaction Terminology (WHO)
WHO-DD	Drug Dictionary (WHO)
WHO-DRL	Drug Reference List (WHO)
WHtR	World Medical Association
WMA	Waist-to-Height-Ratio

WORM	Write Once Read Many
WP	Working Party (EMA)
WTO	World Trade Organisation
WTP	Willingness to Pay
XEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XEVPRM	Extended EudraVigilance medicinal Product Report Message
XML	Exentsible Markup Language

Additional acronyms may be found at
<http://www.abbreviations.com/>

Recommended Reading

Standard Textbooks in Pharmaceutical Medicine

Principles and Practice of Pharmaceutical Medicine. 2nd Edition Edwards. Lionel D; Fletcher, Andrew J; Fox, Anthony W; Stonier Peter. ISBN 978-0-470-09313-9 (John Wiley & Sons 2007)

The Textbook of Pharmaceutical Medicine. J.P. Griffin; J.G. O'Grady. ISBN 0-7279-1523-1 (2002, Publ. BMJ Books)

Drug Research and Development

Pharma 2020: The Vision which Path will you take? Price WaterhouseCoopers (2007) via web www.pwc.com/pharma

The Future of Pharma R&D Challenges and Trends Harald Pacl, Gunter Festel, Günther Wess (Eds.). ISBN 3-00-014012-3. (Festel Capital, 2004)

Guide to Drug Development. A Comprehensive Review and Assessment. Spilker Bert. ISBN 10-7817-7424-1. (Lippincott Williams and Wilkins, 2009)

IBM Global Services: Pharma 2010: The Threshold of Innovation. Arlington S et al. (2004) via Web www.ccm/bcs/pharma 2010

The Investigators Guide to Clinical Research. A step by step guide to becoming a successful clinical investigator. David Gisberg / Robert Whitaker. ISBN 1-930-62430-1 (Pub Center Watch Publications 2002)

Fraud and Misconduct in Biomedical Research. Wells Frank, Farthing Michael (4th edition, Royal Society of Medicine Press, 2008)

A Guide to the Global Pharmaceutical Industry. Mark Greener. ISBN 1-85978-498-4 (Informa Publishing Group Limited 2001)

A Guide to Clinical Drug Research. Cohen Adam M. & Posner John. 2nd edition. ISBN 0-792-36172-5 (Publ Kluwer Academic Publishers 2000)

Expediting Drug & Biologics Development: A Strategic Approach. Ed. Steve Linberg. ISBN 978–1882615766. (Parexel 2006)

Pharmaindustry and Biotech Indsutry

From Alchemy to IPO: The Business of Biotechnology. Robbins-Roth C.Basic Books; 1 edition (April 10, 2001)

Drugs-From Discovery to Approval. Ng, R Wiley-Liss; 1 edition (January 2, 2004)

Science Business: The Promise, the Reality, and the Future of Biotech Pisano G. Harvard Business School Press; 1 edition (November 14, 2006)

The Business of Healthcare Innovation. Burns LR. Cambridge University Press; 1 edition (September 19, 2005)

Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat. Hawthorne F. Wiley; 1 edition (February 25, 2005)

Building Biotechnology: Starting, Managing, and Understanding Biotechnology Companies - Business Development, Entrepreneurship, Careers, Investing, Science, Patents and Regulations. Friedman Y. Thinkbiotech; 2 edition (August 1, 2006)

Science Lessons: What the Business of Biotech Taught Me About Management. Binder G, Bashe P. Harvard Business School Press (April 15, 2008)

Pharmacology and Toxicology

Clinical Pharmacokinetics: Concepts & Clinical Applications. Rowland M. (3rd edition, Lippincott, Williams & Wilkins, Baltimore, March 2006)

Introduction to Pharmacokinetics and Pharmacodynamics. Tozer TN, Rowland M. ISBN 0781-75149-7 (Lippincott Williams & Wilkins, February 2006)

Good Practice of Clinical Drug Trials. Spriet A, Dupin-Spriet P. 3rd edition, revised and expanded. ISBN 3-8055-77249 (Karger Publishers, 2005)

The Practice of Medicinal Chemistry. 2nd edition, edited by Camille Georges Wermuth. ISBN 978-0-12-374194-3 (Academic Press/Elsevier, Amsterdam, 2008)

Goodman & Gilman's The Pharmacological Basis of Therapeutics. ISBN 0-0713-5469-7 (McGraw Hill Publishing 2001).

The Dose Makes the Poison. A plain language guide to toxicology. M Alice Ottoboni. ISBN 0-442-02556-4 (Pub Van Nostrand Rheinhold, 1997)

Presenting Toxicology Results. How to evaluate date and write reports. Gerhard Nohynek. ISBN 07848 0476 7 (Pub Taylor Francis 1996)

Clinical Trial Design

Modelling and Simulation in Clinical Drug Development. Rooney KL, Snoeck E, Watson PA. Drug Discov Today 2001, 6 (15), 802–806

Biomarkers Definitions Working Group: Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework. Clin Pharmacol Ther 2001, 69 (3), 89–95.

Fundamentals of Clinical Trials. Friedman L M, Furberg C D, and DeMets D L. 3rd edition. ISBN 0-387-98586-7 (Springer-Verlag, New York, 1998)

Clinical Trials: A Methodologic Perspective. Piantadosi S. 2nd edition. (John Wiley & Sons 2005)

Clinical Trials: A Practical Approach. Pocock S. (John Wiley & Sons 1996; reprints only: 2002)

Statistical Tables for the Design of Clinical Studies. Machin D, Campbell MJ. (Oxford, Blackwell 1996)

Guide to Clinical Trials. Spilker B. (Lippincott Williamns & Wilkins 1991; reprint only 2000)

The Use of Computer Assisted Design to Support Good Clinical Trials. Snoeck E & Watson MB. Good Clinical Practice Journal Vol 6, No 5

Randomised Controlled Trials: Questions, Answers and Musings, 2nd Edition. Jadad AR, Enkin MW. BMJ Books 2007

Designing Clinical Research; An epidemiologic approach. Hulley SB at al. Lippincott William Wilkins 3rd Ed. 2006

Principles and Practice of Clinical Research, Second Edition (Principles & Practice of Clinical Research). Gallin JI, Ognibene F. Academic Press; 2 edition (May 8, 2007)

Introduction to Biostatistics

Primer of Biostatistics. Stanton A. Glantz. (McGraw-Hill Medical Publishing 2005)

Systematic Reviews in Health Care. Meta-analysis in context. Egger M, Smith GD, Altman DG. ISBN 0-7279-1488-X (2nd edition, BMJ Books 2001)

Statistical Methods in Medical Research. (ICH 9 1999) via Web.

FAQ's on Statistics in Clinical Trials. Grieve AP. (Brookwood Medical Publications 1998)

Using and Understanding Medical Statistics. Matthews DE, Farewell VT. 3rd edition. ISBN 3-8055-6276. (Karger Publishers 1996)

Practical Statistics for Medical Research. Altman DG. ISBN 0-412-27630-5(Chapman and Hall 1991; reprint only: 1999, but 2nd edition anticipated 2007)

How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers Paperback Lang TA, Secic M. American College of Physicians; 2nd edition (December 30, 2006)

Odds Ratio, Relative Risks

Survival analysis. A Self-learning Text. Kleinbaum DG. 2nd edition. ISBN 0-387-23918-9 (Springer 2005)
Statistical Methods in Medical Research. Armitage P, Berry G et al. 4th edition. (2002)
Medical Statistics – A common-sense Approach. Campbell MJ & Machin D. 3rd editon. (John Wiley & Sons 1999)
Applied Regression Analysis and Other Multivariable Methods. Kleinbaum DG, Kupper LL, Muller KE, Nizam A. ISBN 0-534-20910-6 (Duxbury 1998)

Mantel-Haenszel Tests

Statistical Methods for Rates and Proportions. Fleiss JL (page 173). 3rd edition. (John Wiley & Sons 2003)

Sequential and Cross-Over Trials, Bayesian and Frequentist Methods

Statistical Issues in Drug Development. Senn S. (John Wiley & Sons 1997; 2nd edition anticipated 2007)
The Design and Analysis of Sequential Trials. Whitehead J revised 2nd edition. (John Wiley & Sons 1997)

Epidemiology

Epidemiology in Medicine. Hennekens CH, Buring JE. ISBN 0-316-35636-0 (Little, Brown 1987)
Modern Epidemiology. Rothman K, Greenland S, Lash TL. Lippincott Wilkins 2008
Epidemiology. L. Gordis. Saunders; 4 edition (May 14, 2008)

Clinical Epidemiology: The Essentials. Fletcher RH, Fletcher SW. Lippincott Williams & Wilkins; Fourth Edition edition (March 1, 2005)

Health Economics/Pharmacoeconomics/Decision Analysis

Introduction to health economics for physicians. Meltzer MI Lancet 2001;358(9286):993–8

Decision Making in Health and Medicine. Hunink M, Glasziou P. ISBN 0-521-77029-7 (Cambridge University Press 2001)

Methods for the Economic Evaluation of Health Care Programmes. Drummond M et al. Oxford, 3rd Edition 2005.

Designing and Conducting Cost-Effectiveness Analyses in Medicine and Health Care. Muennig P, Khan K Jossey-Bass; 1 edition (March 18, 2002)

Cost-effectiveness in Health and Medicine. Siegel JE, Russell LB, Weinstein MC, Gold MR. ISBN 0-19-510824-8 (Oxford University Press 1996)

Medical Decision Making. Sox H. The American College of Physicians; 1st edition (November 15, 2006)

Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. Petitti DB. Oxford University Press, USA; 2 edition (January 15, 2000)

Other

Glossary of terms used in Pharmacovigilance; WHO Glossary08.doc. http://ebookbrowse.com/glossary-revised-08-doc-d419740300

Useful Websites

International Bodies and Societies

CIOMS. Council for International Organizations of Medical Science. http://www.cioms.ch/
DIA. Drug Information Association. http://www.diahome.org
DPMA. Deutsches Patent- und Markenamt. http://depatisnet.dpma.de
EFPIA. European Federation of Pharmaceutical Industries Associations. http://www.efpia.org
EFSA. European Food Safety Authority. http://www.efsa.eu.int/ In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks regarding food and feed safety.
EMA. European Medicines Agency. http://www.ema.europa.eu/
ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. http://www.encepp.eu/
EPO. European Patent Office. http://worldwide.espacenet.com/
FDA. Food and Drug Administration. http://www.fda.gov/. Entry to FDA guidelines on policy, procedures etc.

Common Website for the Human and Veterinary Medicines Authorities in Europe

HMA. Heads of Medicines Agencies. http://www.hma.eu/
ICH. International Conference on Harmonisation. http://www.ICH.org/ web site for ICH; synopsis of ICH guidelines and topics.
IFAPP. International Federation of Associations of Pharmaceutical Physicians. http://www.ifapp.org
ISO. International Organization for Standardization. http://www.ICH.org/
ISOP. International Society of Pharmacovigilance. http://www.isoponline.org/

NANDO. New Approach Notified and Designated Organisations Information System (List of Notified Bodies in the EC). http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=country.main

OECD. Organization for Economic Co-Operation and Development. http://www.oecd.org/ehs/

RAPS. Regulatory Affairs Professionals Society Europe. www.raps.org

USPTP. United States Patent and Trademark Office. www.uspto.gov/

WHO. World Health Organisation. http://www.who.int/. World Health Organisation, headquarter home page

Regional Office for Europe. http://www.who.ch/ http://www.who.dk

WHO Collaborating Centre for International Drug Monitoring Uppsala, Sweden. http://www.who-umc.org

WMA. World Medical Association Inc. (Declaration of Helsinki). http://www.wma.net.

Schools and Bodies Providing Postgraduate Training for Pharmaceutical Physicians

ACRP. Association of Clinical Research Professionals. www.acrpnet.org.

Cardiff University, BrAPP course. http://www.cardiff.ac.uk/phrmy/degreeprogrammes/postgraduate/pharmaceuticalmedicine/index.html. http://www.cardiff.ac.uk/pharmy/index

DGPM. Deutsche Gesellschaft für Pharmazeutische Medizin. (*former FÄPI*, Fachgesellschaft der Ärzte in der Pharmazeutischen Industrie). www.dgpharmed.de

ECPM. European Center of Pharmaceutical Medicine. http://www.ecpm.ch/

EUCRAF. European Center for Regulatory Affairs Freiburg. http://www.eucraf.eu

GPM. Gesellschaft für Pharmazeutische Medizin e.V. http://www.gpmed.at homepage of the Society for Pharmaceutical Medicine (Austria)

MEGRA. Mitteleuropäische Gesellschaft für Regulatory Affairs e.V. http://megra.org

SGPM/SwAPP. Schweizersche Gesellschaft für Pharmazeutische Medizin. www.sgpm.ch and www.swapp.ch

ULB. Université Libre de Bruxelles / Vrije Universiteit Brussel. http://medinfo.ulb.ac.be/pharmed.

Medical Websites, Dictionaries, Codes and Other Science Oriented Web Sites

http://invention.swmed.edu/argh. acronyms and abbreviations; world's largest and most comprehensive catalogue of biomedical acronyms and abbreviations with nearly 260,000 entries;

http://www.medlexicon.com. acronyms and abbreviations; contains around 200.000 abbreviations and acronyms, but also links to search engines like allhealthnet.com, web sides of pharmaceutical companies, hospitals, professional associations, health ministries, directories, journals, and consulting companies with e-mail, fax- and phone numbers or other useful information.

http://www.infobiogen.fr/services/chromcancer/index.html. atlas on chromosomes involved in cancer;

http://www.reviewscience.com. antimicrobial database about antimicrobial activities of pharmaceutical drugs and of compounds occurring in nature; AMICBASE(−EssOil) displays the antimicrobial spectra of drugs, antibiotics, compounds produced by higher plants etc.

http://www.madgc.org. autoimmune diseases; website maintained by a group of leading genetic researchers who have joined efforts to identify and understand the genes that autoimmune diseases have in common;

http://www.orpha.net/consor/cgi-bin/index.php portal of rare diseases and orphan drugs;

http://www.hon.ch/HONselect/RareDiseases/ list of rare diseases with terms in English, French, German, Spain and Portuguese.

http://www.dimdi.de/germ/klassi/icdg/fr-icdg.htm. classification of diseases (ICD); website of DIMDI (Deutsches Insitut für Medizinische Dokumentation und Information) with access to the International Classification of Diseases ICD-10 (in German) and all older versions of the ICD (downloadable);

http://www.cochrane.org. The Cochrane Collaboration, an international not-for-profit organization, providing up-to-date information about the effects of health care;

http://dietary-supplements.info.nih.gov/Health_Information/IBIDS.aspx. dietary supplements data base; over 700,000 citations on dietary supplements; source of information on vitamin, mineral, phytochemical, botanical, and herbal supplements in human nutrition;

http://afen.onelook.com. dictionary; 13,090,565 words in 1100 dictionaries indexed, including special medical terms, glossary of oncology terms, etc.

http://www.yourdictionary.com. dictionary with definitions, thesaurus entries, spelling, pronunciation, and etymology results; one can browse the English dictionary alphabetically or by related terms to find meanings and synonyms. In addition, YourDictionary provides resources to find the best dictionary and translation sites for French, Spanish, Italian, German and hundreds of other languages; about every language on the world can be found here, from Bengali to Lithuanian; the site includes both language and specialised dictionaries (medicine, law etc.) and 96 grammars;

http://www.hyperdictionary.com/medical/ Medical Dictionary providing explanations of various medical terms and diseases.

http://www.cancer.gov/dictionary/ Dictionary of Cancer Terms; contains more than 4,000 terms related to cancer and medicine

http://www.virtualhealthlibrary.org/php/index.php?lang=en. homepage of the Virtual Health Library; provides access to databases of Medline, Cochrane etc.

http://www.merck.com/mrkshared/mmanual/ Merck Manual; searchable access to The Merck Manual with a lot of information such as normal laboratory values, disease,

http://rxlist.com. medicinal products; a very complete searchable crossindex of almost 5,000 US prescription products, OTCs and nurtraceuticals; permits fuzzy search for generic or brand name drug but also for NDC code search and medical abbreviations.

http://www.whocc.no/atc_ddd_index/ a searchable version of the complete ATC index with DDDs maintained by WHO; search options enable to find ATC codes and DDDs for substance name and/or ATC levels;

http://www.hardlink.com/~tsute/bacteria/index.html microbiology; information on many aspects of microbiology incl. bacterial genera

http://www.bacterio.cict.fr microbiology; list of prokaryotic names with standing in nomenclature (LPSN); hyperlinked information such as descriptions of a particular species/genus and references;

http://www.oecd.org/ OECD, Organisation for Economic Co-operation and Development

http://www.lenntech.com/periodic-chart.htm periodic table – chart of all chemical elements;

http://www.mhc.com/Cytochromes/Links.HTML P450 and P-glycoprotein Drug Interactions Web Sites;

http://medicine.iupui.edu/clinpharm/ddis/ cytochrome P450 Drug Interactions table;

http://www.cypalleles.ki.se/ home page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee, allele nomenclature for Cytochrome P450 enzymes;

http://www.rarediseases.org website of the National Organisation for Rare Disorders (NORD) with information on 1,150 diseases that can be accessed in a free or subscription version;

http://medicine.wustl.edu/%7Evirology viruses; information on viruses, incl. structure and biology;

http://www.eudrapharm.eu a database for independent information about all medicines, both human and veterinary, available to Europeans, no matter whether these medicines have been authorised at EU or national level.

http://www.healthcalculators.org/index.html free access to various risk calculators such as for diabetes.

http://www.ehealthme.com/drug_interactions_checker drug interactions checker, operated free of charge by *eHealthMe*, identifies drug interactions, side effects, and interacting drugs.

Important Guidelines

EMA
http://www.emea.eu.int/index/indexh1.htm. Website of the EMEA for the latest updates of Community/ICH guidelines (Regulatory Guidance and Procedures – Notes for Guidance).
www.ema.europa.eu/Inspections/index.html. GMP, GCP or GLP inspections

EU
European Union http://ec.europa.eu/health/documents/eudralex/index_en.htm. EudraLex – The Rules Governing Medicinal Products in the European Union.

FDA
http://www.gpoaccess.gov/CFR/. Code of Federal Regulations
www.fda.gov/RegulatoryInformation/Guidances/default.htm. FDA Guidances
www.fda.gov/ora/compliance_ref/part11. Office of Regulatory Affairs. Compliance References: Title 21 CFR Part 11
www.21cfrpart11.com. www.21cfrpart11.com/files/library/government/21cfrpart11_final_rule.pdf. 21 CFR Part 11

Other
Declaration of Helsinki. http://www.wma.net/e/policy/b3.htm
Common Toxicity Criteria. http://ctep.cancer.gov/reporting/ctc.htm
Drug Development and Drug Interactions. http://ctep.cancer.gov/reporting/ctc.html
Common Technical Document. http://www.ich.org/cache/compo/1325-272-1.html - http://www.fda.gov/cber/gollns/m4ctd.pdf