Gerhard Nahler

Dictionary of Pharmaceutical Medicine

Springer-Verlag Wien GmbH

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Foreword by Gerhart Hitzenberger

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Dr. med. Dr. phil. Gerhard Nahler
CIS Clinical Investigation Support Pharmaforschung
Vienna, Austria

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Foreword

The evolution of pharmaceutical medicine, clinical pharmacology and drug therapy has over the last few years led to the creation of a large number of new terms and their abbreviations with the result that physicians and pharmacists are at a loss when confronted with these terms. This is also due to the fact that everything connected with pharmaceutical medicine is based on interdisciplinary knowledge introduced by specialists in widely differing fields.

The present book is most welcome, as it gives short and precise information on nearly all questions. Statistics, clinical pharmacology with its different branches, issues of clinical drug investigation and pharmacotherapy as such are dealt with. Definitions of individual terms reflect, of course, the present state and will need to be continuously updated as to their meaning.

This book is therefore most suitable for students of pharmacy and medicine as well as pharmacists and physicians as a source of quick and conclusive information. I therefore hope that this publication will meet with success and widespread approval.

Univ.-Prof. Dr. Gerhart Hitzenberger
Österreichische Arbeitsgemeinschaft
für Klinische Pharmakologie

Preface

Pharmaceutical medicine nowadays is a multidisciplinary area comprising aspects of toxicology, pharmacology, statistics, drug-regulatory and legal affairs, medicine and a number of other disciplines. Therefore it is necessary to acquire additional knowledge to whatever one has studied or done at the beginning. Although post-graduate formation is offered by an increasing number of institutions, training in the field of pharmaceutical medicine is largely "on the job" and done mainly by the pharmaceutical industry or contract research organisations. Many years of experience with new colleagues showed me how useful some sort of booklet might be, that would give them a better understanding of some of the less familiar technical terms and their context. In this dictionary, containing at present more than 800 keywords, the attention of the user is drawn to such relationships by cross-references printed in small capitals.

In addition, it is always a difficult decision as to whether to include citations or not and there was a great temptation to make references throughout the text to important publications especially those of health authorities. However, this would certainly have been beyond the scope of a brief dictionary intended for daily use and I find it absolutely necessary that the user familiarises him- or herself with original, complete texts and specific, original literature for further information and not only with a compilation of citations. As a consequence, some important documents are listed in the back matter of this book. It was after all these deliberations that the idea of producing this particular type of short dictionary in its present form was born.

As is the problem with almost all dictionaries, information given therein must be short. Furthermore, the discipline of pharmaceutical medicine is in permanent evolution and growing. This makes it difficult to keep such a dictionary "complete" and up-to-date. In addition, this dynamic process also leads to differences in an individual's understanding and utilisation of one and the same term. It will certainly occur that one person, also among readers, might interpret or define some terms differently from another. I beg therefore the user's indulgence of these aspects and invite their comments.

A further important aspect is the utilisation of abbreviations. Technical jargon usually tends to create its own abbreviations, and this is also true for the field of pharmaceutical medicine. A separate register of more than 800 frequently used abbreviations is therefore included.

Finally a directory of important national and international bodies and organisations as well as authorities completes the back matter. This may help to establish contacts and to get further information.

This dictionary is aimed primarily at the beginner entering this discipline or coming into occasional contact with pharmaceutical medicine as part of his/her daily work, as is the case with investigators, researchers in the pharmaceutical industry, people in marketing departments, drug regulatory affairs or governments. I hope however that the content will also be of interest to experienced colleagues in departments engaged in clinical development.

As everybody knows, it is impossible to write such a dictionary without the helpful criticism of experienced colleagues and friends. I wish therefore to acknowledge many of comments and useful discussions with Dr Dominique B., Dr Bob Nolan and Dr Axel Wenzel in the initial stages of this book. I should also like to thank for the permission to reproduce some of the definitions and addresses cited in this book.

Gerhard Nahler

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abbreviated new drug application 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.

Aberdeen drug coding system see CODE.

absolute risk see RISK.

accelerated approval program 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 NEW DRUG APPLICATION.

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 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; results may be accurate, i.e. lying within acceptable boundaries, but still imprecise, because they are widely scattered; see MEASUREMENT PROPERTIES, PRECISION.

acknowledgements Authors of publications frequently use a. to thank persons who made technical or intellectual contributions 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 daily jobs without any special contributions.

active ingredient Pharmacologically active part(s) of a FORMULATION; the maximum acceptable deviation in the a.i. content of a finished product must not exceed ±5% at the time of manufacture.

activities of daily living 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-treated analysis see PER-PROTOCOL ANALYSIS.

actuarial method see SURVIVAL ANALYSIS.

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

additive effect see INTERACTION OF DRUGS, ERROR.

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.

admission criteria see ELIGIBILITY CRITERIA.

adverse drug event (ADE) see ADVERSE REACTION, CONCOMITANT EVENT, DRUG INJURY, PHARMACOVIGILANCE.

adverse drug experience (ADE) Can either be *expected (labeled)* which means that the event is listed in the current (FDA-) approved labeling for the drug as a possible complication of drug use or *unexpected (unlabeled)*, the latter term includes an event that may differ from a labeled 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 labeling; see also ADVERSE DRUG EVENT, LABELING.

adverse drug reaction (ADR) 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; see also ADVERSE REACTION, DRUG INJURY.

adverse event (AE) 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 ASSESS-

MENT 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; see also ADVERSE EXPERIENCE, CONCOMITANT EVENT, PHARMACOVIGILANCE, SAFETY UPDATE REPORT.

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

adverse reaction (ADR) Reaction which seems to be causally related to intake of a pharmaceutical product and which is "noxious, unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function"; *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*: serious = ADR which is "LIFE-THREATENING, requires inpatient hospitalization, prolongs hospitalization, permanently or severly disabling, or requires prescription drug therapy: the following types are always considered serious: death, congenital anomaly, cancer, or overdose" (FDA); *classification:* type A = "augmented", reactions of a predictable nature, following a known response pattern; type B = "bizarre", effects that are unpredictable (hypersensitivity or idiosyncratic reactions); EC regulations foresee *reporting* of (spontaneous) serious ADRs (labelled or unlabelled) to the competent authority within 48 hours of their receipt by the company (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 within 15 calendar days (FDA: working days), including assessment of *causality;* a second type of report are periodic reports (EC: half-yearly for the first two years of marketing and annually thereafter for the first 5 years, than every 5th year; FDA: quarterly for the first three 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* = that is "not listed in the current labelling for the drug as having been reported or associated with the use of the drug" (FDA); this includes an ADR that may be symptomatically or pathophysiologically related to a known ADR, but differing in nature, severity or incidence (frequency) with regard to information given in the current labelling, e.g. PACKAGE INSERT, INVESTIGATOR'S BROCHURE, in the general INVESTIGATOR'S PLAN, or elsewhere; methods for assessments are e.g. voluntary reporting, intensive drug surveillance or case-control studies; see also ADVERSE EVENT, CAUSALITY, DRUG INJURY, CRITICAL TERM LIST, WHO COLLABORATING CENTER FOR INTERNATIONAL DRUG MONITORING, WHO-ADVERSE REACTION TERMINOLOGY, WHO-DRUG REFERENCE LIST.

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."

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.

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 > 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.

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).

analysis see EXPLANATORY TRIAL, EXTENDER A., INTENT-TO-TREAT A., PER-PROTOCOL A.

anatomical therapeutic chemical classification system (ATC) Recommended by the WHO for use in drug utilisation studies; drugs are divided into different groups and codified according to their main site of action as well as therapeutic and chemical characteristics; ATC-codes may be updated; useful also as basis for setting up therapeutic groups for REIMBURSEMENT; see also WHO-DRUG REFERENCE LIST.

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.

antagonism see INTERACTION OF DRUGS.

approval Authorisation for marketing a new product; see also COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS.

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".

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.

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.

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

attributable risk see RISK.

audit 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 national law, 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; 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 on production plants and laboratory facilities to ensure adherence to GOOD MANUFACTURING PRACTICE (GMP) or GOOD LABORATORY PRACTICE (GLP) respectively; see also ACCEPTABLE QUALITY LEVEL, CONFIDENTIALITY, ESTABLISHMENT INSPECTION REPORT, ISO/DIS 10011-2, MEDICAL A.

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

audit trail see DATA TRAIL.

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).

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.

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; see also CODE.

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 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 selected at random, with not less than 3 batches to be taken for assessment of batch-to-batch variability; see also LOT.

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".

benefit-risk analysis see DECISION ANALYSIS.

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): $A > \text{or} < B$, 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, GAMMA ERROR.

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

bias ERRORS due to incorrect assumptions; 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; *changing pattern* b. = methods of diagnosis, techniques, treatments a.s.o. may change over time; *selection (sample distortion)* b. = selected cases may not represent adequately the whole population; *confounding* b. = one or more variable associated, independently of exposure, both with exposure and outcome; *reverse causality* b. = study outcome preceded and caused actually the exposure; *publication* b. = studies with positive, statistically significant results are more likely to be published, which may result in overestimation of treatment results; principal b. reducing techniques are BLINDING and RANDOMIZATION; see also DRUG CHANNELLING, ERROR, HAWTHORNE EFFECT, INTENT-TO-TREAT A., LABELLING PHENOMENON, PLACEBO EFFECT, REGRESSION PARADOX, SEQUENCE EFFECT.

bioavailability Extent and rate of absorption of a DRUG from a given dosage form into the systemic circulation; examples of factors on which the b. depends are: 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 PHARMACOKINETIC.

bioequivalence Drugs with the same BIOAVAILABILITY are considered as bioequivalent.

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

biological medicinal products Products such as vaccines, serums, toxins, ALLERGEN PRODUCTS and medicinal products derived from human blood or plasma.

biological products 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).

black list List produced by the FDA which contains the names of INVESTIGATORS who are "ineligible to receive investigational products" (Feb. 1993: 79 names); an additional list contains the names of "investigators agreeing to some restriction of their use of investigational products" (Feb. 1993: 28 names); see also INVESTIGATIONAL DRUG.

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.); 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 ensurance of b.; see also DOUBLE-DUMMY TECHNIQUE; DISCLOSURE PROCEDURE.

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.

body-mass-index (BMI) For calculating the ideal weight; BMI = body weight (in kg) divided by (height × height) (in m) should be between 20 to 25; example: w = 76 kg, h = 1.82 m; 1.82 × 1.82 = 3.3; 76 / 3.3 = 23; see also LORENTZ-FORMULA.

body surface The body surface area a (in m^2) can be calculated by the following formula: 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.

Bonferroni correction In order to avoid ERRORS by repeated significance testing the SIGNIFICANCE LEVEL is divided, as a rule of thumb, by the number of comparisons (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; see also INTERIM ANALYSIS.

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

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.

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".

CANDA Computer assisted new drug application, whereby the information on the new DRUG is submitted in electronic form; no universal recommendations exist at the time being.

CAPLA Computer assisted product licence application; see CANDA.

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

carcinogenicity tests see TOXICITY TESTS.

carry-over effect see SEQUENCE EFFECT.

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; 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 nondiseased 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 nonsmokers 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.

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; see also LETHALITY.

case record form (CRF) syn. case report 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 or optical disk methods or any other means, ensuring accurate input and allowing verification against RAW DATA; CRFs are to be considered as documents; EC: "CRFs may be requested by Member States and should therefore always be available"; see also PATIENT DIARY.

case report form (CRF) see CASE RECORD FORM.

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

categorical data see DATA.

causality syn. imputability; in some 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 required, 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; 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 STANDARDIZED ASSESSMENT OF CAUSALITY.

ceiling effect opp. FLOOR EFFECT; treatment effects or scores that can be reached are limited, even when dosage or treatment duration a.s.o. is increased (e.g. analgetics).

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 ETHICS COMMITTEE reviewing a PROTOCOL for different institutions, e.g. in a multicentre or multinational trial; in some countries, e.g. Austria, approval by the ethics committee of each participating hospital is requested; in other countries, e.g. France, approval by one central e.c. is sufficient.

centralised procedure syn. CONCERTATION PROCEDURE, former high technology procedure; procedure in the EC for getting marketing authorization esp. for high technology medicinal products (products of significant therapeutic interest or innovation), in particular for those derived from biotechnology (obligatory for products developed by recombinant DNA technology, monoclonal antibody methods etc. for which 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 and CPMP resp. is undertaken by the RAPPORTEUR member state to which the pharmaceutical company applies for marketing authorization; examination by the CPMP takes place at the same time as examination of the application by authorities of the rapporteur member state which initiated the procedure; bio/high-tech applications are likely to be treated as exceptional with the period of review being 210 days; products will automatically benefit from a ten 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.

changing pattern see BIAS, CUSUM PLOT.

chemical equivalents see PHARMACEUTICAL EQUIVALENTS.

chirality Drugs with a carbon atom to which 4 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 antiarhythmic, L-thyroxin is a hormone whereas D-thyroxin is a lipid-lowering substance, only L-thalidomid causes embryotoxic effects, 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; see also DISTOMER, ENANTIOMER, EUTOMER.

CIOMS form Reporting form for adverse reactions; as a mini-

mum 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; see also ADVERSE DRUG REACTION.

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); see also CREATININE CLEARANCE, 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.

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 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, some of these activities may be delegated to a "STUDY NURSE"; see also MONITOR.

clinical research coordinator (CRC) see CLINICAL TRIAL 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.

clinical research organisation (CRO) see CONTRACT RESEARCH ORGANISATION.

clinical significance see DELTA VALUE.

clinical study 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"; 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 4 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; see also DESIGN, MEDICAL OFFICE TRIAL, MULTICENTRE TRIAL, RUN-IN PHASE.

clinical trial authorisation (CTA) Formal approval to do studies; in some countries formal approval by health authorities to do studies esp. with experimental drugs is requested (at least for the very first application of a new drug in man), e.g. US, UK, Austria, France, most countries in Eastern Europe a.s.o.; 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 EXEMPTION.

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) In large and complex trials it may be suitable to nominate a CTC who coordinates dates for visits, investigations a.s.o.

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 notification (CTN) see CLINICAL TRIAL AUTHORISATION.

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.

close down see TERMINATION VISIT.

close out visit see TERMINATION VISIT.

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 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.

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.

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

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.); 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 nonrandomly 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.

coinvestigator see INVESTIGATOR.

co-marketing see CO-PROMOTION.

combining of lab data see POOLING OF LAB DATA.

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 MULTISTATE PROCEDURE, CENTRALISED PROCEDURE.

Committee on Safety of Medicines (CSM) Committee preceding the MEDICINES CONTROL AGENCY (MCA); official body concerned with EFFICACY and SAFETY aspects of new MEDICINAL PRODUCTS.

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

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.

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, single, named patient treatment; "pilot" application of a DRUG; 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, other than early safety DATA; there must be very careful observations and reporting on outcome made; see also EXPANDED-ACCESS PROGRAM, TREATMENT IND.

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 DM 500,000.00 per patient or of DM 10,000,000.00 per trial respectively; see also CLINICAL TRIAL COMPENSATION GUIDELINES, INDEMNIFICATION, INSURANCE, PRODUCT LIABILITY.

compliance Degree of adherence of a patient to therapeutic advice or the dosage schedule resp.; about 2/3 of the patients (non-compliers) do not take medications as prescribed (time, frequency, dose, duration a.s.o.); 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 a.s.o.; regardless of the degree of compliance all patients initially included in studies should be reported (INTENT-TO-TREAT principle).

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.

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.

conditional approval syn. restricted marketing authorization; usually a time-limited approval on SURROGATE ENDPOINTS, HISTORICAL CONTROLS or other type of limited information; further clinical studies (e.g. POST-MARKETING SURVEILLANCE) may be a condition of marketing APPROVAL and required by health authorities.

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%); c.i. give 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).

confidence limits see 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 ...".

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 nonexperimental 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 nonexperimental 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 PLACEBO EFFECT, LEARNING EFFECT.

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 one year over a one year period a.s.o.; see also MEASUREMENT PROPERTIES.

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

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 pairwise comparisons and for multiple groups, paired samples the modified F-test; see also DATA.

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, 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).

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 DESIGN, MÜNCH'S LAW.

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 licence may be allowed to prescribe a c.d.; see also GENERAL SALE LIST MEDICINE, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE, GRAS-LIST.

co-promotion syn. co-marketing; one DRUG is promoted by two or more companies under a single TRADEMARK; c.-p. achieves greater visibility in the marketplace and makes entry of new competitive drugs more difficult; see also JOINT-MARKETING.

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.

correlation coefficient (r) 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:

$$r = \Sigma\ (x_i - \bar{x})\ (y_i - \bar{y})\ /\ \sqrt{\Sigma\ (x_i - \bar{x})^2\ \Sigma\ (y_i - \bar{y})^2};$$

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.

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); 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 and Canada, but not by the FDA); see also DELTA VALUE.

cost/effectiveness analysis (CEA) 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.

cost/minimisation analysis (CMA) Compares costs of treatments which have identical medical outcomes; 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) 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 UTILITY MEASUREMENT, QUALITY OF LIFE.

Council for International Organisation of Medical Sciences (CIOMS) International, non-governmental, non-profit organisation; 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-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.

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.

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.

cross-over see DESIGN, HEATON-WARD EFFECT.

cross-sectional study 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; 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 COHORT STUDY, CASE-CONTROL STUDY.

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.

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.

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* (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 pseudo-continuous 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, OUTLIERS, RAW D.

data analyst see DATA MANAGER.

data archiving see ARCHIVING.

data audit trail see DATA TRAIL.

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.; this ensures consistency across 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 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; 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. (opposite: *batch* input), 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 beginn of the d.e. process a data entry screen, matching the CRF as close as possible, has to be prepared.

data lock-point (DLP) syn. cut-off date; date at which a data base is "frozen" in order to follow development of stored information, e.g. every 6 months subsequently to the date of the first approval by the first regulatory authority for a particular drug; see also SAFETY UPDATE REPORT.

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 center, 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 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.

data resolution form (DRF) syn. CRF correction log, 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 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.

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

death rate see MORTALITY RATE.

decentralised procedure Formerly multistate procedure; to make it easier for obtaining marketing authorization in at least two further EC member states by a common application after first having obtained marketing authorization in one member state (afterwards "RAPPORTEUR"); the initiating national authority submits its assessment report to other member states and to the COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP); the authorities of these member states have 120 days to grant authorization to market the product in their country or to formulate reasoned objections; in this case the matter is referred to the CPMP which considers the grounds for objections as well as explanations (written or oral) provided by the applicant; within 60 days the CPMP issues its own reasoned opinion which is addressed to the member states concerned and to the applicant; within a further 60 days the member states must decide on what action to take pursuant to the CPMP's opinion and must inform the CPMP on their decision; the multi-state proce-

dure relates only to medicinal products authorised in accordance with the criteria laid down by the directives of the EC; see also CENTRALISED 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 favorable 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.

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) and Hong Kong (1989).

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.

delta value 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.

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

design *Cross-over d.* (opp. parallel) = two period or multiperiod comparison (within- or between-SUBJECT); each subject receives two treatments one after the other (or simultanously 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 a 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); 80% of the positive results reported in studies *without control* (i.e. without further parallel group(s) for direct comparison) cannot 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); *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; 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 GEHAN'S DESIGN, NON-COMPARATIVE STUDY, OBSERVATIONAL STUDY, ONE SAMPLE MULTIPLE TESTING DESIGN, RANDOMIZED CONSENT D., REPEATED MEASURES D., SEQUENTIAL D.

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.

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 Pharmacopoea, (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, hemodialyzers; examples for class III d.: heart valves, inflatable penile implant, electrohydrolic lithotripter; see also DEVICE MASTER RECORD, MEDICAL DEVICE.

device master record (DMR) FDA: "compilation of records containing the design, formulation, specifications, complete manufacturing procedures, quality assurance requirements and labeling 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, labeling, 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.

diagnostic index Frequency of patients with a specif 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 RECRUITMENT RATE.

diary card see PATIENT DIARY.

dichotomous data see NOMINAL DATA.

diploma in pharmaceutical medicine In some countries (e.g. Belgium, Mexico, Spain, 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 Term used for documents in the EC which are legally binding in contrast to a GUIDELINE; see EC LAW.

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.

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 "impairements" (neurologic abnormalities), "disabilities" (physical incapacity), and "handicaps" (societal impact); see also ILLNESS.

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

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; see also DISINTEGRATION TEST, FORMULATION.

distomer see CHIRALITY, ENANTIOMER.

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.

dose escalation study Application of increasing doses of a new substance in human subjects in PHASE I trials; 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 9 escalations (e.g.: 1, 2, 3.3, 5, 7, 9, 12, 16 mg/m^2); generally about 3 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.

dose response relationship In general, the EFFECT of a DRUG can be considered to be proportional to its dose; the documenta-

tion of such a relationship is important in early investigations of drug effects; effects with biological substances as e.g. interferons may go through an optimum, i.e. decreasing with increasing doses; see also PHASE I.

dosing schedule see TREATMENT SCHEDULE.

double blind see BLINDING.

double data entry see DATA ENTRY.

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.

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 (lost to follow-up) 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); in long-term trials the d-o. rate will be at least 4% per annum but the overall d.-o. rate should not exceed 20%; in a three 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; see also EXTENDER ANALYSIS, INEVALUABILITY RATE, RUN-IN PERIOD, WITHDRAWALS.

drug FDA: (1) substance recognized in the Official US Pharmacopea, Official Homeopathic Pharmacopea, 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).

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 dependence WHO: "a state, psychic and sometimes physical, resulting from the interaction between a living organism and a DRUG, characterised by behavioral 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 experience report Report on an ADVERSE REACTION; see also REPORT.

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.

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.

drug monitoring (1) continuous measurements of drug concentrations in biological fluids or tissues for therapeutic or safety reasons; (2) 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 FORMULATION.

drug safety monitoring (DSM) Active surveillance for drug safety (in contrast to SPONTANEOUS REPORT SYSTEM); see also POST-MARKETING SURVEILLANCE, YELLOW CARD PROGRAMME.

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

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.

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 have no legally binding character at all.

economic analysis syn. pharmacoeconomic study; overall term for analyses such as COST/EFFECTIVENESS A., COST/UTILITY A., and QUALITY OF LIFE studies; 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"), European regulatory authorities are expected to follow in 1995; in 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).

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; see also 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 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; 5–10 subjects will normally be sufficient to generate significant results; see also SAMPLE SIZE ESTIMATION.

efficacy 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.)"; see also EFFECT, EFFECTIVENESS.

elderly Subjects older than 65 years; see GERIATRIC EVALUATIONS, HEALTH CARE COSTS.

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 informations, 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 choosen 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 PHASE of a CLINICAL TRIAL (tight during early phases of development, loose in late phases); see also INCLUSION C., EXCLUSION C.

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 INSTITUTIONAL REVIEW BOARD (IRB) approval; FDA regu-

lations require that e.u. is reported to the IRB within 5 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.

EN 29000 see ISO 9000.

enantiomer STEREOISOMERS which are similar to mirror images of each other; enantiomers which are pharmacologically active are called distomers, those which are inactive, eutomers; see also CHIRALITY, STEREOISOMER.

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

enrollment list see PATIENT IDENTIFICATION LIST.

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.

epidemiology def.: study of the distribution of DISEASES or ADVERSE EVENTS in human populations, and of the factors which influence this distribution; see also EXTRA INCIDENCE RATE OF NON-VACCINATED GROUPS.

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., GAMMA E., DATA, MEDICATION E., RAW-DATA, OUTLIERS.

error of measurement (E of M) see ERROR.

essential drug list (EDL) 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.

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.

ethical drug 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 STEERING COMMITTEE.

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.

European Medicines Evaluation Agency (EMEA) Planned registration authority within the EC, sited in London.

European Pharmacopoeia (Eur Ph) Pharmacopoeia published by the Council of Europe.

eutomer see CHIRALITY, ENANTIOMER.

evaluation report see AUDIT.

excipient see FORMULATION.

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; see also INCLUSION CRITERIA, ELIGIBILITY CHECKLIST.

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.

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 review FDA allows e.r. for certain kinds of research involving no more than minimal RISK (e.g. recording data from adults by noninvasive 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 report Each EC MULTISTATE or HIGH-TECH application for marketing authorization shall contain three e.r., both 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).

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 STABILITY TESTS.

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

expiry date 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".

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 PRAGMATIC/DECISION-MAKING TRIAL; PILOT STUDY.

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; see also ANALYSIS.

extension protocol see CONTINUATION STUDY.

external audit 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.

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.

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 NEW DRUG APPLICATION.

FDA 483 form Form used in the USA for inspectional observations; see INSPECTION.

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; 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; see also CIOMS FORM.

Fibonacci search scheme see DOSE ESCALATION.

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.

finished product EC (IV): "a MEDICINAL PRODUCT which has undergone all stages of production, including packaging in

its final container"; see also BULK PRODUCT, INTERMEDIATE PRODUCT, PACKAGING, PRODUCTION, STARTING MATERIAL.

first-pass effect Metabolism of a DRUG before it can reach the systemic circulation, most often due to metabolism in the liver, but possibly also on other sites as e.g. the lung, or the gastronintestinal 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).

floor effect opp. CEILING EFFECT; effects, especially SCORES measured, cannot go beyond a predefined lowest level; therefore observations will accumulate and form a rather inhomogenous group.

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, chewing gum, and article used as component of any such article.

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

forced licensing see COMPULSORY LICENSING.

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; *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 gelatin; capsules enclose the drug as powder or non-aqueous liquid within their two halfs; *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; see also LIPOSOME, PRODRUG.

fraud In science fraud occurs most often as *trimming*, (involves discard of DATA of the extremes so that they look cleaner), *cooking* (ignoring 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 DATA DREDGING.

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 obvious; example: if with an antitumor DRUG no response occurs among the first 14 SUBJECTS, then the hypotheses of a response rate $\geq 20\%$ 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 prespecified 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.

general sale list medicine (GSL) Drug which may be sold at any shop (UK); see also CONTROLLED DRUG, GRAS-LIST, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE.

generic Short term for 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.

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

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.

genotoxicity Toxic effects upon genetic material (DNA) of cells, inducing permanent and transmissible damages in the amount and/or structure of the DNA; 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, GENOTOXICITY, MICRONUCLEUS TEST, TOXICITY TESTS.

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"; 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.

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; see also GOOD CLINICAL TRIAL PRACTICE.

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 1 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"; 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 ISO 9000, QUALIFIED PERSON.

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.

good regulatory practice (GRP) Standards for regulatory practices.

GP trial see MEDICAL OFFICE TRIAL.

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 $A\alpha$, $B\beta$, $C\gamma$, group 2 $B\gamma$, $C\alpha$, $A\beta$ and group 3 $C\beta$, $A\gamma$, $B\alpha$.

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.

guideline Term used for documents in the EC which are not legally binding, in contrast to a DIRECTIVE; see EC LAW.

half life ($t_{1/2}$) Time within which half of a substance has been eliminated from the body (time taken for plasma concentrations to fall by 50%); see PHARMACOKINETIC, TREATMENT SCHEDULE.

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

Hawthorne effect Study participation per se affects the outcome, especially behavioral measures are subject to this effect; see also BIAS, LABELLING PHENOMENON, PLACEBO EFFECT, WHITE-COAT HYPERTENSION.

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 costs The US health care system has at present the highest costs in the world with 14% of the gross domestic product (GDP); European systems cost between 7% and 9% of the GDP (Germany 8%); in western countries about 35 to 50% of these costs are expended for the ELDERLY; see also PRICE REGULATORY SCHEME.

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.

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

Heaton–Ward effect Subjective assessments can be severly 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.

Helsinki declaration see DECLARATION OF HELSINKI.

herbal medicines see PHYTOMEDICINES.

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, constitue a significant innovation, (2) medicinal products administered 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 selec-

tion, diagnostic techniques, environmental conditions a.s.o.; see also BIAS, CONTROL, MINIMIZATION, MATCHED PAIRS.

hospital file see PATIENT FILE.

Huriet see LOI HURIET.

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

ideal body weight see LORENTZ FORMULA.

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 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.

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.

imputabilty see CAUSALITY.

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

incidence rate def.: number of SUBJECTS who, over a specific time, develop a specific attribute/total number of subjects; see also PREVALENCE RATE.

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.

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

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 10 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 3 working days (5 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.

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

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 to 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.

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 both parents and the child may give their consent) 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; FDA 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 fetus, 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 PATIENT INFORMATION SHEET, RANDOMIZED CONSENT DESIGN.

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 Relevant authorities (e.g. in US, France etc.) may conduct official inspections of clinical INVESTIGATORS, SPONSORS, INSTITUTIONAL REVIEW BOARDS and laboratories in order to verify adherence to regulations and 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 publicised, 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 assessement" = directed at those facilities not previously inspected; the result of the inspection is the ESTABLISHMENT INSPECTION REPORT; see also FDA 483 FORM, FDA 484 FORM.

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 5 members, with varying backgrounds, possessing the necessary professional competence, including at least one member from a nonscientific 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"; at present usual limits for indemnity are in Germany DM 500,000.00 for each research subject (examples for max. amount of coverage: Germany: DM 10,000,000.00/event, Italy: Lit 5,000,000,000.00, UK: £ 5,000,000.00); see also COMPENSATION FOR DRUG INDUCED INJURY, INDEMNIFICATION, PRODUCT LIABILITY.

intensive research design see SINGLE CASE STUDY.

intent-to-treat analysis syn. intention-to-treat a., pragmatic a., management a., effectiveness a.; opp. actual-treated a., PER-PROTOCOL 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; usually both types of analyses are provided for randomised CLINICAL TRIALS; per-protocol a. are more likely to be subject to BIAS; see also EXPLANATORY TRIAL, INEVALUABILITY RATE.

intent-to-treat list syn. patient log list, patient log book, patient 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 judgements 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.

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.

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

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. 10 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 3 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.

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 Date on which the first regulatory authority granted marketing authorisation of a new drug; see also MARKETING EXCLUSIVITY.

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

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 speciality of pharmaceutical medicine as well as on the development and use of medicines; from its beginnings in 1972 to now 26 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. TRADE NAME); recommended by the WHO; in 1991 this WHO-list contained 6,085 INNs, (1988: 5,520); contrasts with e.g. local official names as British Approved Names (BAN), United States Adopted Names (USAN), JAN etc.

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

intervention trial syn. prevention trial; trial studying prevention of DISEASE.

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 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 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 production or 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 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 two 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; *primary* (or *principal*) i.: one single person who supervises or coordinates a trial and who is responsible for the medical and scientific conduct of a multicentre study, the p.i. might not actually

also conduct the investigation (coinvestigator) or dispense the TEST ARTICLE (subinvestigator) 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; *coinvestigator* means equal and shared responsibility for the conduct, control, and completion of a study; each coi. complets his own Form FDA 1572, item 1; *subinvestigator* 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 dispension 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 ..."; see also STUDY COORDINATOR.

investigator's brochure syn. 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 during the course of the trial if new data arise; see also PRETRIAL DATA.

investigator's drug brochure see INVESTIGATOR'S BROCHURE.

investigator's manual see INVESTIGATOR'S BROCHURE.

investigator's meeting see PRESTUDY MEETING.

ISO 9000/EN 29000 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; see also GOOD MANUFACTURING PRACTICE.

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.

ISO/DIS 10011-2 Guidelines for auditing quality systems – qualification criteria for auditors (1989); see also AUDIT.

joint-marketing One product is sold by two companies under two TRADEMARKS; see also CO-PROMOTION.

Kaplan–Meier method syn. product-limit method; see SURVIVAL ANALYSIS.

Karch and Lasagna classification see 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% = severly 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.

Korotkoff sound 1st sound: 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 intraarterial pressures; also the pressure at which pulse of arteria radialis/brachialis reappears); 4th sound: point of muffling of sounds, i.e. when the sounds stop to have a tapping character; 5th sound: complete disappearance of the sound (recorded as diastolic pressure).

Koseisho Japanese health ministry.

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, expiry date, producer; 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, INVESTIGATIONAL DRUG LABELLING, LABEL TEXT.

labelling phenomenon Means that the patient experiences an increased number of subjective symptoms (depression of mood, tiredness etc.) after being informed of his/her diagnosis of e.g. hypertension; 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.

label text Requirements for label texts of 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 state-

ments etc., lot no., expiry date, bottle no., study no., patient no., name of investigator, name of manufacturer, address of manufacturer; texts may be requested to be in local language; see also LABELLING.

label use American term for use of a drug for its approved indications.

laboratory normal range syn. reference range; each laboratory has its own ranges within which values or results of a specific test can be considered as "normal", i.e. unpathologic; 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.

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.

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.

learning effect syn. practice e.; see SEQUENCE EFFECT; see also CONFOUNDER, PLACEBO EFFECT, LABELLING PHENOMENON.

lethality Number of subjects dying from a specific disease divided by the number of subjects suffering from this disease; see also MORBIDITY, MORTALITY, CASE FATALITY RATE.

LD-10 Dose 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).

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 costs of launching and establishing a new product are 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; 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 NEW CHEMICAL ENTITY, RESEARCH AND DEVELOPMENT.

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 it occurred in a more serious form, might have caused death."

Likert scale Usually a 3 or 5 point SCALE for CATEGORICAL DATA.

linear analogue self assessment (LASA) see VISUAL ANALOGUE SCALE.

linear correlation coefficient (r) see CORRELATION COEFFICIENT.

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.

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 FORMULATION.

literature controls see HISTORICAL CONTROL.

loading dose Initial dose of a DRUG which is higher than the MAINTENANCE DOSE; the concept being to achieve a therapeutic concentration more rapidly (e.g. therapy with tetracyclins, digitalis glycosides).

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.

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 BODY-MASS-INDEX.

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.

magistral 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.

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".

marketing application see NEW DRUG APPLICATION.

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 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 HIGH-TECH MEDICINAL PRODUCTS, INTERNATIONAL BIRTH DATE, ORPHAN DRUG.

marketing study Studies which are conducted in order to promote a product; such studies are more and more 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.

masking see BLINDING.

master file see TRIAL MASTER FILE.

master plan see STUDY LIST.

master record see DEVICE MASTER RECORD.

matched pairs see MINIMIZATION, RANDOMISATION.

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 non-lethal dose (MNLD) Highest single dose which does not induce death in animals; has replaced calculation of LD-50 values.

maximum repeatable dose (MRD) Dose which provides the

first evidence of significant toxicity whereby the substance is administered in increasingly larger dosages – each three to four days – to the same group of animals; see also TOXICITY TESTS.

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 NOEL, TOXICITY TESTS.

mean Arithmetic mean: average of a number of values (the sum of the values divided by the number of observations); if the DATA are normally distributed the mean and MEDIAN coincide; see also MODE, DISTRIBUTION, STANDARD ERROR.

measurement properties ACCURACY, CONSISTENCY, PRECISION, RELIABILITY, REPRODUCIBILITY, VALIDITY, VARIABILITY.

median midmost value of a distribution; 50% of n observations have higher, and 50% lower values, therefore = (n + 1) / 2; see also MEAN, MODE, DISTRIBUTION.

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.

medical culture Differences in medical culture and traditions are especially important when running MULTINATIONAL TRIALS or when comparing their results; examples for such differences: the number of prescriptions per person in 1987 was: 19.3 in Italy, 12.2 in Germany, and 7.3 in UK (expenditures on PRESCRIPTION medicines per head, 1990: Italy 157 $, Germany 142 $, UK 82 $); the dosage of drugs in Japan is about a quarter of that in US; mean duration of hospitalization (1987, in days): Netherlands 35, Switzerland 25, Germany 17, UK 15, Italy 11, Denmark 9; in 1980 in US and UK only about 25% of general surgeons and 5% of orthopedic surgeons reported using subcutaneous heparin routinely, whereas in Sweden, more than three quarters of general surgeons and one third of orthopedic surgeons did; in France 2.55% of all patients receiving a prescription get lipid lowering drugs in contrast to 0.98% in Germany, 0.80% in Italy and 0.05% in UK; in Italy prescription of suppositories is more frequent than in Germany, the French worry about their livers, the English about their bowels a.s.o which is reflected also by the percentage of spontaneous reports on adverse reactions: in

France, 8.4% of all reports in the WHO-database concern liver reactions in comparison to 1.6% in Irland; see also BIAS, PRESCRIPTION.

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"; see DEVICE, INVESTIGATIONAL DEVICE EXEMPTION, MEDICAL DEVICE REPORTING.

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; reporting of death or serious injury has to be done to the FDA 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 office trial syn. GP trial, usually a MULTICENTRE TRIAL, done in general practice or other non-hospital units.

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 to 15% of the cases; see also ERROR.

medicinal product EC (I): "any substance or combination of substances presented for treating or preventing DISEASE in human beings or animals"; see also BULK PRODUCT, FINISHED PRODUCT, INTERMEDIATE PRODUCT, PACKAGING MATERIAL, PROCEDURES, PRODUCTION.

Medicines Control Agency (MCA) UK licensing authority, responsible also for CLINICAL TRIAL EXEMPTION or CLINICAL TRIAL CERTIFICATE; supported by other committees as the CSM, SEAR.

mee-too see INNOVATIVE CHEMICAL EXTENSION.

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).

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.

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.

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. 3/4); used in comparisons to (historic) controls, rarely also as alternative to RANDOMIZATION.

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.

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.

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.

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 studies or 200 case report forms per year according to good clinical practice.

monitor's visit log list syn. site visit log; list kept by the investigator in which each visit by the monitor or clinical research associate is entered and usually also signed off.

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.

Muench's law see MÜNCH'S LAW.

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; 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 DIS-

EASE, 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.

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).

mutagenicity tests see TOXICITY TESTS.

NAFTA see NORTH AMERICAN FREE TRADE AGREEMENT.

named patient use see TREATMENT IND.

negative list List of medicines which are excluded from reimbursement by national healthcare or insurance systems resp.

network chart see PROGRAM EVALUATION TECHNIQUE.

new active substance (NAS) see NEW CHEMICAL ENTITY.

new chemical entity (NCE) syn. new active substance, new molecular entity; according to estimates made in 1990, the average NCE takes 12 years from synthesis to marketing approval, costs $ 231 million, and needs 19 years of worldwide sales to recover RESEARCH AND DEVELOPMENT investment; 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 (with an increasing trend), 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 synthesised to one NCE marketed is about 2,000 : 1 to 6,000 : 1; see also INNOVATIVE CHEMICAL EXTENSION, LIFE CYCLE MANAGEMENT, RESEARCH AND DEVELOPMENT.

new drug application (NDA) Application for marketing approval; review for NDA by the FDA takes about 20 to 30 months and costs which are charged by the FDA may be in the order of 500,000.00 $; see also FDA 356H FORM.

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.

NLN see NORDIC COUNCIL OF MEDICINES.

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 abbr. no-effect level in chronic toxicity studies with animals, i.e. highest tested dose without toxic effects.

no-fault insurance Guarantees compensation for persons injured, distressed or subjected to unnecessary pain or suffer-

ing as a result of activities comprising the CLINICAL TRIAL 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.

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-comparative study syn. open study; unblinded 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 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 without spontaneous cure (e.g. gonorrhea, treatment with suitable antibiotic); see also CLINICAL TRIAL.

noncompliance see COMPLIANCE.

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 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.

non-prescription drug see OVER-THE-COUNTER.

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 one year before the EC guidelines; 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 $.

notes for guidance 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.

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.

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.

Nutley system glossary see CODE.

observational study Nonexperimental, open label, uncontrolled study, often done in PHASE IV; 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; see also NON-COMPARATIVE STUDY.

odds The o. of a specific event is the ratio of the probability of its occurrence divided by its probability of nonoccurrence; see META-ANALYSIS.

odds ratio Ratio of two ODDS; o.r. is a good estimate of the true relative risk of exposure in the target population, provided outcome is rare; 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 American term for use of a drug in other than approved indications (opp. LABEL USE).

ointment see FORMULATION.

old see GERIATRIC EVALUATIONS.

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.

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.

on-site audit see AUDIT.

open study see NON-COMPARATIVE STUDY, UNBLINDED STUDY.

optical activity see CHIRALITY.

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, hierar-

chical 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.

orphan drug DRUG for a narrow indication; in US a drug may be designated and registered as o.d., receiving a seven years marketing exclusivity (Japan: 10 years) if the number of patients will not exceed an estimated maximum of 200,000 cases in a year (Japan: 50,000); a subsequent drug considered to be similar must be clinically superior in order to receive marketing exclusivity; a "shared" (with another company) exclusivity can be granted; in 1991, 52 drugs (in 61 indications) were approved as o.d.; the estimated number of such "rare" DISEASES is about 5,000; 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); see also EXPANDED-ACCESS PROGRAM.

outcome measurement syn. outcome VARIABLE; see ENDPOINT.

outliers DATA that have been incorrectly recorded; 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.

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.

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, PHARMACY DRUG, PRESCRIPTION ONLY MEDICINE, GRAS-LIST.

package insert see PATIENT INFORMATION LEAFLET.

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".

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.

parallel design see DESIGN.

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.

parametric test Statistical test assuming a defined distribution of the DATA, e.g. a NORMAL DISTRIBUTION.

partition coefficient (pK_a) Is a measure of lipid solubility of a DRUG; determines the uptake under un-ionised conditions; see also PHARMACOKINETIC.

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; see also MARKETING EXCLUSIVITY, CENTRALISED PROCEDURE, INTERNATIONAL BIRTH DATE.

patient diary syn. patient report form; form on which patients record their subjective observations concerning a treatment; sometimes used in OUTPATIENT studies; 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 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 Sometimes called enrollment list; the investigator must be able to identify the patient by its code; it is necessary therefore to have a list exhibiting the codes as well as the complete identification of each patient (surname, given name, date of birth); EC guidelines request also that the participation of a patient is marked in the medical records; see INVESTIGATOR.

patient information leaflet (PIL) syn. PATIENT PACKAGE INSERT, PATIENT PRODUCT INFORMATION; provides general information for patients on the correct use of a drug; in most countries PILs are compulsory and controlled by the health ministries; some countries (e.g. Austria, Germany, France) differentiate 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 INTENT-TO-TREAT LIST.

patient log list see INTENT-TO-TREAT 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 the annually published Physician's Desk Reference; see also PATIENT INFORMATION LEAFLET.

patient register see PATIENT IDENTIFICATION LIST.

patient report form (PRF) see PATIENT DIARY.

patient screening log see INTENT-TO-TREAT LIST.

Parouzzi principle "Given a bad start, trouble will increase at an exponential rate."

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.

Pearson correlation coefficient (r) see CORRELATION COEFFICIENT.

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 status 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 self-care 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.

periodic site visit syn. routine monitoring visit; usually the MONITOR OR CLINICAL RESEARCH ASSOCIATE visits the trial site every 4 to 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.

per-protocol analysis syn. actual-treated a.; only patients finishing the study according to the protocol are analysed, DROPOUTS and WITHDRAWALS are excluded; opp. INTENT-TO-TREAT ANALYSIS.

Perussel's law "There is no job so simple that it cannot be done wrong."

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 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 manufac-

ture 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; see MANUFACTURER.

pharmacodynamic Science dealing with the (pharmacologic) mechanism of drug action once it reaches the target organ(s).

pharmacoeconomic study see ECONOMIC ANALYSIS.

pharmacoepidemiology Science of systematic or observational studies of DRUG EFFECTS in populations receiving the drug through usual clinical practice; p. deals 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 Science studying people with unusual metabolism.

pharmacokinetic Science dealing with the absorption, distribution, metabolism, and excretion (ADME) of DRUGS in the body; see also AREA UNDER THE CURVE, BIOAVAILABILITY, CLEARANCE, FIRST-PASS EFFECT, HALF LIFE, PARTITION COEFFICIENT, PROTEIN BINDING, VOLUME OF DISTRIBUTION.

pharmacology Science dealing with effects of a drug on organs or body systems.

pharmacopoeia Regularly updated information on drugs in book form (standards of 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.

pharmacovigilance Used often synonymously to POST-MARKETING SURVEILLANCE; system for collecting spontaneous REPORTS on ADVERSE REACTIONS, assessing CAUSALITY and RISKS; adverse reaction frequencies are expressed as cases per treatment or per month of treatment sold; knowledge of drug sales is essential; although spontaneous reporting is the most com-

monly used method, either voluntary as e.g. in UK or compulsory (e.g. Austria, France), whereby either the physician has to report directly to the health authority (Austria, France, Italy) or the pharmaceutical company (Germany, USA); one of the major drawbacks 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; see also DRUG SAFETY MONITORING, POST-MARKETING SURVEILLANCE, SAFETY OFFICER, YELLOW CARD.

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 I First trials 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 to 80, the mean development time 16 months (1987); commonly used target doses in phase I trials are e.g. 1/3 of the TOXIC DOSE LEVEL (TDL) in the most sensitive large animal species, or 1/10 of the LD-10 in the mouse and 1/3 of the TDL in dogs, or 1/3 of the LD-10 in mice; see also ADME, DOSE ESCALATION, FIBONACCI SEARCH SCHEME, LATIN SQUARE DESIGN.

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.

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 longterm safety studies; usually several hundred to several thousand subjects are included in MULTICENTRIC, often MULTINATIONAL studies; generally the circumstancies 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"; 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 definiton 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, nonblinded 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 POST-APPROVAL RESEARCH.

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); in Europe, Germany is at present the largest market for p. covering about 70% of the total consumption; see also SELF-MEDICATION.

pill-counting see COMPLIANCE.

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 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.

placebo Experimental preparation which has the same appearance as the active drug but which contains no pharmacologic active substance(s); a p. should not be 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; 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.

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.

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.

population attributable risk see ETIOLOGIC FRACTION.

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 to 45% of NCEs approved between 1970 and 1987 had PAR requests, the trend is increasing; see also POST-MARKETING SURVEILLANCE.

post-marketing surveillance (PMS) syn. PHARMACOVIGILANCE; 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; often the approach is retrospective which might then cause severe bias; 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; major methods are: spontaneous, voluntary reporting schemes (e.g. YELLOW CARD system), intensive hospital monitoring, use of official statistics and observational, nonexperimental studies such as CASE-CONTROLLED STUDIES, COHORT STUDIES, PRESCRIPTION-EVENT MONITORING, PRESCRIPTION SEQUENCE ANALYSIS; in some EC member states, e.g. 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.

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%.

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.

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.

predictive value Proportion of those patients with a positive (negative) test who are diseased (not diseased), see also SENSITIVITY, SPECIFICITY.

pregnancy see LABELLING, WOMEN.

preinvestigation visit see PRESTUDY VISIT.

premarketing trial see PHASE IIIB.

premedication Medication taken till start of therapy with a study DRUG.

prescription In 1990, French patients received on average 38 prescription items/year, compared with 20.1 in Italy, 7.6 in UK, and 4.2 in The Netherlands; per capita annual spending

on medicines was about 300 DM in Italy, 290 DM in France, 270 DM in Germany, 180 DM in The Netherlands, and 160 DM in UK; see also MEDICAL CULTURE.

prescription-event monitoring (PEM) Multiple COHORT scheme; technique collecting DATA from field use of a medicine without disturbing prescribing decisions or patient selection; PEM is an accepted method for post-marketing surveillance.

prescription only medication (POM) (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.

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".

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.

prestudy meeting syn. INVESTIGATORS meeting; especially in MULTICENTRE trials, the MONITOR has not only to make sure that investigators and their staff have understood the PROTOCOL and the isssues 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.

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/total number of subjects; see also INCIDENCE RATE.

prevention trial see INTERVENTION TRIAL.

price control Prices of medicinal products are controlled by health authorities; products must have their own realistic prices, calculated on the basis of their real costs and using transparent methods of calculation.

price regulatory scheme (PPRS) 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 to 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.

primary endpoint Also called key data, key (efficacy) criteria, hard endpoints; outcome VARIABLES which are considered as especially important for postulating a clinically meaningful difference (death, 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.

principal investigator see INVESTIGATOR.

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".

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 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"; see also COMPENSATION FOR DRUG INDUCED INJURY, INDEMNIFICATION, INSURANCE.

product licence (PL) Approval to advertise, supply and sell a MEDICINAL PRODUCT.

product-limit method see KAPLAN–MEIER METHOD.

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) 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.).

promoter see SPONSOR.

promotional trial see MARKETING TRIAL.

proprietary medicinal product (PMP) opp. GENERIC.

proprietary name see TRADE NAME.

protein binding Many drugs bind to plasma proteins but only

the unbound fraction is available for diffusion to the site of action; 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.

protocol syn. study plan, 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"; 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.

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.

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".

qualified person (QP) In order to be eligible for manufacturing authorization pharmaceutical firms must employ the following key personal: a production manager, a control manager (responsible for quality control/drug testing), a sales manager; they may be the same person in special cases; proof of the expert knowledge is generally requested; see also GOOD MANUFACTURING PRACTICE.

quality-adjusted life-years (QALY) syn. healthy-year equivalent (HYE); 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 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 QUALITY CONTROL.

quality control Operational techniques and activities to ensure that a trial is in compliance with the principles of GOOD CLINICAL PRACTICE; it operates upon all members of the investigational team (clinical staff, SPONSOR, CONTRACT RESEARCH ORGANISATION etc.) involved with planning, conducting, monitoring, evaluating, and reporting a trial including DATA processing, with the objective to establish and protect the credibility of data, to improve the ethical, scientific and

technical quality of a trial, to avoid false conclusions being drawn from unreliable data and to avoid exposure of trial subjects to unnecessary risks; elements of q.c. are e.g. SOURCE DATA VERIFICATION, DATA TRAIL, internal and external AUDITS; q.c. applies also to the MANUFACTURE and 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.

quality of life (QL, QoL) Measurements relating 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), psychologic state, emotional life and social interaction, and somatic sensation; this definition is therefore based on both subjective (SYMPTOMS, general well-being) and objective judgements (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 HEALTH-RELATED QUALITY OF LIFE, PERFORMANCE STATUS, COST/BENEFIT ANALYSIS, WELL-BEING SCALE.

quality of life scale Examples are: KARNOFSKY PERFORMANCE STATUS, SF-36 (36 item short form of the Medical Outcome Study MOS), Spitzer's Quality of Life Index (QLI, for patients with cancer and chronic diseases), Sickness Impact Profile (SIP, esp. for more healthy people), Profile of Mood States (POMS), Psychological General Well-Being Index (PGWB,

for the emotional domain of quality of life), EORTC Quality of Life Questionnaire (EORTC-QLQ), 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.

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.

Quetelet 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.

racemate see CHIRALITY.

radiopharmaceutical EC (I): "any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose".

randomization SUBJECTS are allocated to two or more treatments by mere chance; appropriate 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.; procedures as just mentioned do not allow any external control, the trialist is 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 (favorite 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 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. 3/4) 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 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.

rapporteur Original 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 has been ad-

dressed 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 .

rate syn: proportion; differences and rates are common summary measures.

rating scale see SCALE.

raw data Records or certified copies of the original clinical and laboratory findings from the trial; term is sometimes used as a synonym for data in CASE RECORD FORMS; see also SOURCE DATA VERIFICATION.

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 after abrupt withdrawal of a drug e.g. after stopping antihypertensive treatment with clonidine blood pressure may "overshoot" in rare cases.

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; see DECHALLENGE, SINGLE CASE EXPERIMENT.

rechallenge trial see DESIGN.

reconciliation EC (IV): "a comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used".

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.

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 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.

reference range see LABORATORY NORMAL RANGE.

regression coefficient see LINEAR REGRESSION.

regression paradox syn. regression toward the mean, statistical regression; spontaneous variations of symptoms or diseases make judgements 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.

regulation see EC LAW.

reimbursement see COST/EFFECTIVENESS, DEFINED DAILY DOSE, ANATOMICAL THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM, QUALITY OF LIFE.

relative risk see RISK.

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.

repeatability Level of agreement between replicate measurements made in the same subject; see also MEASUREMENT PROPERTIES.

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 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. BASELINE comparison of treatment groups, number of subjects RANDOMIZED, 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); according to EC guidelines of good clinical practice (III) r. of clinical trials have to be archieved 5 years beyond the life time of the product; see also IMRAD.

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".

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, TOXICITY TESTS, LABELLING.

research and development (R&D) The average NEW CHEMICAL ENTITY (NCE) costs about $ 230 million (estim. 1990) and takes 12 years (1987) from synthesis to marketing approval (about 3 years in the 1960s); this includes costs of failed projects and time costs (mean development times: longterm animal studies 33.6 months, phase I 15.5 months, phase II 24.3 months, phase III 36.0 months, NEW DRUG APPLICATION review by FDA 30.3 months); 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 15,000 million US $ in 1988 (24,500 million in 1992), therefore almost doubling every 5 years, with 61 NCEs approved (35 in 1989); the 100 top R&D companies had 2976 drugs in research or development phases; each additional week of clinical development accounts for a loss of sales revenues in the order of $ 1–2 million; worldwide ethical pharmaceutical sales were in the order of $ 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 DEVELOPMENT, HEALTH CARE COSTS, LIFE CYCLE MANAGEMENT.

research nurse see STUDY NURSE.

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, POST-MARKETING SURVEILLANCE.

return EC (IV): "sending back to the MANUFACTURER or distributor of a MEDICINAL PRODUCT which may or may not present a quality defect".

risk *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); *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 ASSOCIATION TRIAL.

risk-benefit analysis see DECISION ANALYSIS.

risk factor Independent VARIABLE in ASSOCIATION STUDIES; the r.f. often precedes the outcome (dependent variable).

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.

routine monitoring visit see PERIODIC SITE VISIT.

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 to 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.

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.

safety officer EC proposals foresee that each company has a permanent person in a member state responsible for PHARMACOVIGILANCE.

safety tests Toxico-pharmacological test, as well as tests on sterility, bacterial endotoxin, pyrogenicity, and local tolerance.

safety update report (SUR) Some regulatory authorities (e.g. EC) request regular collection of ADVERSE DRUG REACTIONS (foreign and domestic, sometimes 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 SURs should be prepared at six-month intervals, within 45 calendar days of the DATA LOCK-POINT, for all NEW CHEMICAL ENTITIES licensed for the first time in 1992 and thereafter; 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; see also ADVERSE EVENT, TRANSITION MATRIX.

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 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 deter-

mines 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.

sanctions Regulatory actions that apply to devices, their manufacturers and distributors, when they are discovered to be in violation of FDA requirements: detention, seizure, FDA initiated or voluntary recall, regulatory letter, citation, injunction, and prosecution.

scales Instruments for measuring "hard-to-quantify" variables, i.e. non-dimensional, ORDINAL DATA; a number of different types exist, e.g. LIKERT SCALE, faces s., VISUAL ANALOGUE s., ladder 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 INDEX, ORDINAL SCALE, QUALITY OF LIFE SCALE, WELL-BEING SCALE.

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).

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 INDEX, SCALES.

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-medication opp. prescription-only medication; see 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 SPECIFICITY, PREDICTIVE VALUE.

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, analgetics, 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.

side effects see ADVERSE DRUG REACTIONS, DRUG INJURY.

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 is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

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.

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 SYMPTOMS.

sign test Simple, nonparametric statistical test for specific sets of data (characteristic quality is present or not).

single-blind see BLINDING.

single case experiment Also N of 1 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-site trial syn. single center 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 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.

SNOMED Systematized Nomenclature of Medicine, see CODE.

source data Patient files, original recordings from automated instruments, tracings (ECG, EEG), X-ray films, laboratory notes a.s.o.; see also 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".

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 SENSITIVITY, PREDICTIVE VALUE.

sponsor syn. promoter; organization or individual who takes responsibility for the initiation, management and/or financing of a trial; responsibilities (FDA): "... for selecting quali-

fied 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, 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).

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 quantitate 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.

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 $\sqrt{r}$ times as many patients to B than to A.

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 $25 \pm 2\,^{\circ}C$, at $60 \pm 5\%$ relative humidity, with 3 batches, and for a minimum of 12 months; see STRESS TESTING.

standard deviation (SD) Square root of the sum of squares of deviation divided by one less than the number of squares in the sum

$$\sigma = \sqrt{\Sigma\,(x_i - \bar{x})^2 \,/\, (n-1)};$$

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.

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 immediatly 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 interobserver variability; 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 may also be a suitable method; see ADVERSE DRUG REACTION.

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.

standard operating procedures (SOP) Preestablished, systematic written procedures for the management, organisation, conduct, data collection, documentation and verification especially of CLINICAL TRIALS; SOP should describe the step-by-step actions necessary to initiate and complete the task required in each job description; SOP assure correctness, consistency and completeness in an operation and shorten training periods; EC guidelines request that sponsors "establish detailed SOPs to comply with GOOD CLINICAL PRACTICE" (or GOOD LABORATORY PRACTICE, GOOD MANUFACTURING PRACTICE resp.) and that the monitor "works according a predetermined SOP".

starting material EC: "any substance used in the production of a MEDICINAL PRODUCT, but excluding PACKAGING MATERIALS".

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.

stereoisomer Molecules differing only in their three-dimensional (geometric) structure but not in their chemical composition and formula; see CHIRALITY, ENANTIOMER.

sterility EC (IV): "absence of living organisms"; (conditions of the sterility test are given in the European Pharmacopoeia).

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).

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; the purpose is to determine kinetic parameters, and to predict the tentative expiration dating period/stability of a drug; stress testing conditions usually include temperature (e.g. 5 °C, 50 °C, 75 °C), humidity (e.g. 75% or greater), 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.

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 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 protocol, for observation of regulatory aspects, for the progress of the study, and finally for analysing and reporting the results.

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.

study list syn. masterplan, clinical program outline; table

where all studies (according to a preestablished 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.

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.

study plan see PROTOCOL.

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.

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 5 subgroups such as male/female, age $\leq 65 / > 65$, 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.

subinvestigator see 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.

substantial evidence FDA: "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effective-

ness 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 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; 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; see also PATIENT INFORMATION LEAFLET.

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.

supportive data Information on efficacy and safety not accepted as PIVOTAL and therefore not central to NEW DRUG APPLICATION.

surrogate endpoint Instead of the (clinical) event itself an event directly related to it is recorded, that indicates presence or worsening of a clinical condition, 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.

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 necessar-

ily 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.

symptoms Subjective indicators of a DISEASE as e.g. pain, tiredness, loss of appetite, anxiety a.s.o.; see also SIGNS.

synergism see EFFECT MODIFIERS, INTERACTION of drugs.

systematic error see ERROR.

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 (minutes or hours) as e.g. for histamine.

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.

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.

therapeutic equivalent Dosage form exhibiting the same EFFICACY (toxicity) when administered in the same appropriate dosage regimen; see also BIOLOGIC EQUIVALENT, PHARMACEUTICAL EQUIVALENT.

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.

time-event schedule see FLOW CHART.

time trade-off 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.

TNM-staging Widely used classification system which is based

on the size of the primary tumour T (To–T4), degree of local spread to lymphnodes N (No–N3, Nx) and distant spread of metastases M (Mo–M3).

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.

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 NOEL.

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); 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.* (subacute, chronic t.) the top dose is chosen so that it produces some minimal adverse effect (e.g. reduction in rate of bodyweight gain) and dose/response relationship can be examined (2 species of mammals, one of which must be a non-rodent); for products to be administered once only to humans, a test lasting 2 to 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 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; such 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 figures can be given (EC):

Human treatment	Toxicity studies
one/several doses, 1 day	2 weeks
repeated doses up to 7 days	4 weeks
up to 30 days	3 months
> 30 days	6 months

a complete toxicity program costs about 5 to 10 million US$ and may use about 5,000 animals; see also GENOTOXICITY, LD-10, MAXIMUM TOLERATED DOSE.

toxicokinetic Relates body drug concentrations and their kinetics to toxicological findings.

trade name syn. proprietary name, brand name; name used together with a trade mark or the name of the manufacturer (opp. INTERNATIONAL NON-PROPRIETARY NAME, GENERIC NAME); 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.n. throughout the Community, unless a justification to do otherwise is given; in most countries the t.n. is liable to revocation after 3–5 years of non-use.

transdermal patch Special formulation where the drug is absorbed through the skin, e.g. nitroglycerin, nicotin a.s.o.

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).

Before	After			
	lowered	normal	raised	total
lowered	9	5	0	14
normal	27	29	14	70
raised	0	45	41	86
total	36	79	55	170

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. 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; see also PHARMACOKINETIC.

treatment use see TREATMENT IND.

trial see CLINICAL TRIAL.

trial design see DESIGN.

trialist see INVESTIGATOR.

trial master file (TMF) syn. 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.

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.

type I error see ALPHA ERROR.

type II error see BETA ERROR.

type III error see GAMMA ERROR.

unblinded study syn. open s.; study where both physician and patient know the treatment.

uncontrolled study Study without CONTROL group.

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.

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"; see also QUALIFICATION.

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 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 MEASUREMENT PROPERTIES, RELIABILITY, QUALIFICATION.

Vancouver style of citation Many scientific journals have agreed to accept papers submitted according to the format described in the paper: "Uniform requirements for manuscripts submitted to biomedical journals" BMJ 1991, 302: 338–341.

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, a.s.o.; see also ACCURACY, MEASUREMENT PROPERTIES.

variable syn. parameter; event, characteristic or attribute that is measured in a study; see CONFOUNDER, COVARIATE, DATA.

variance Describes the spread (variability) of MEASUREMENTS; e.g. differences among SUBJECTS within the same group (intra-group v.); square of the STANDARD DEVIATION (SD × SD); see also REPRODUCIBILITY, VARIABILITY, VARIATION.

variation see COEFFICIENT OF VARIATION.

visit 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. ORDINAL SCALES; see also SCALE, QUALITY OF LIFE SCALE.

volume of distribution (V_d) Apparent volume into which a DRUG would distribute at equilibrium; the V_d is markedly effected by the binding of the drug, e.g. to serum proteins; see also PHARMACOKINETIC.

volunteer A subject participating in a PHASE I clinical trial is usually called a healthy volunteer.

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.

weight see BODY-MASS-INDEX, LORENTZ FORMULA, QUETELET'S INDEX.

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 QUALITY OF LIFE SCALE, HEALTH PROFILE.

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 with new terms added as necessary; WHO-ART is built up as a tree structure ("organ class", "high level term", "preferred term"); it comprises approx. 1,300 preferred terms; synonyms are included at the input side ("included terms") 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., altogether 30 system organ classes; preferred terms are grouped into high level terms which are more general terms for similar

conditions; 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.

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 which are sent by the physician (also dentist or coroner) or company to national centres, usually health authorities, and by them at three month intervals, to the WHO Collaborating Centre in Uppsala; up to now, this system operates in more than 35 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; see also YELLOW CARD PROGRAMME.

WHO-drug dictionary (WHO-DD) Computerised dictionary available on magnetic tape or diskette; updatings are on a quarterly basis; see WHO-DRUG REFERENCE LIST.

WHO-drug reference list (WHO-DRL) 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.

WHO-performance status see PERFORMANCE STATUS, ORDINAL SCALE.

WHO-toxicity scale A 5-grade system (0–4) for reporting of acute and subacute toxic effects of cancer treatment.

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, RUN-IN PERIOD; (2) pharmaceutical products withdrawn from sale; between 1961 and 1987 at least 77 drugs have been withdrawn for safety reasons; see also REBOUND EFFECT.

withdrawal trial see DESIGN.

within-subject design syn. within patient 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; 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.

work breakdown structure (WBS) Hierarchical organisation of tasks; see also PROJECT MANAGEMENT.

World Health Organisation (WHO) Currently more than 180 states are members of the WHO.

yellow card programme SPONTANEOUS REPORTING SCHEME of notification of suspected ADVERSE REACTIONS to drugs (in contrast to active DRUG SAFETY MONITORING) established 1964 and operated by the Committee on Safety of Medicines (CSM) in UK; the system is completely voluntary whereby physicians but also dentists and coronors are encouraged to report; see also PHARMACOVIGILANCE, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING.

Abbreviations/acronyms

AA Application Area
āā ana partes aequales (to identical parts)
AAA (1) Acute Anxiety Attack; (2) Alcoholics Anonymous Association; (3) Abdominal Aortic Aneurysm
AADA Abbreviated Antibiotic Drug Application (FDA)
Ab (1) Antibody; (2) Abortus
ABEMIP Association Belge des Médecins de l'Industrie Pharmaceutique (also BEVAFI) (Belgian society of physicians in the pharmaceutical industry)
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)
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
ADE (1) Adverse Drug Event, Adverse Drug Experience; (2) Acute Disseminated Encephalitis
ADEPT Antibody-Directed Enzyme Prodrug Therapy
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
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
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 Francaise pour l'Assurance Qualité (French Association for Quality Assurance)
AFEC Association Francaise pour l'Etude du Cancer (Paris)
Ag Antigen
AGIM Association Générale de l'Industrie du Médicament
AHA (1) American Heart Association; (2) Area Health Authority
AHF Antihaemophilic Factor
AI Artificial Intelligence
AICRC Association of Independent Clinical Research Contractors
AIDS Aquired Immune Deficiency Syndrome
AIM Active Ingredient Manufacturer
AIMD (1) Active Implantable Medical Device; (2) Active Ingredient Manufacturer
AIMS Arthritis Impact Measurement Scale
AINS Antiinflammatoire Non-Stéroidique (= NSAID)
AL Acute Leukaemia
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
AMG Arzneimittelgesetz (Medicines Act, Austria, Germany)
AMI Acute Myocardial Infarction
AMIP Association des Médecins de l'Industrie Pharmaceutique
AML Acute Myelogenous Leukaemia
AMM Authorisation de Mise sur le Marché
ANCOVA Analysis of Co-Variance (covariate adjustment)
ANDA Abbreviated New Drug Application
ANF Antinuclear Factor
ANOVA Analysis of Variance
AOA American Osteophathic Association
AOD Arterial Occlusive Disease
APA American Psychiatric Association

APMA Australian Pharmaceutical Manufacturers Association
APPA Australian Pharmaceutical Physicians Association
APUA Alliance for the Prudent Use of Antibiotics
AQL Acceptable Quality Level
AR Airway Resistance
ARC (1) AIDS Related Complex; (2) Assistant de la Recherche Clinique (syn. CRA)
ARDS Adult Respiratory Distress Syndrome
ARF (1) Acute Respiratory Failure; (2) Acute Renal Failure
ART Adverse Reaction Terminology (WHO)
ASA (1) Acetyl Salicylic Acid; (2) Adam Stokes Attack; (3) American Society of Anesthesiologists
ASC Altered State of Consciousness
ASCII American Standard Code for Information Interchange
ASCO American Society of Clinical Oncology
ASI Anxiety Status Inventory
ATC (1) Anatomical Therapeutic Chemical Classification System; (2) Animal Test Certificate
AUC Area Under 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)
BGA Bundesgesundheitsamt (German Federal Health Office, Berlin)
BHF British Heart Foundation
BI Broca Index
BID Bis In Die (two times daily)
BIRA British Institute of Regulatory Affairs
BL Burkitt Lymphoma
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
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
CAFVP Cyclophosphamide, Adriamycine, 5-Fluorouracil, Vincristine, Prednisone
CAG (1) Coronary Angiography; (2) Carotid Angiogram
CAHD Coronary Atherosclerotic Heart Disease
CALS Cyclophosphamide, Adriamycine, Methotrexate, Procarbacine
CANC Cancellation (FDA: inspection not conducted)
CANDA Computer Assisted New Drug Application
CAO Coronary Artery Occlusion
CAOS Cosmogen (Actinomycine D), Adriamycine (Doxorubicine), Oncovine (Vincristine), Sendoxane (= Endoxan + Cyclophosphamide)
CAPLA Computer Assisted Product Licence Application
CAPLAR Computer Assisted Product Licensing Application Review (US)
CAS Chemical Abstract Service
CBA Cost Benefit Analysis
CBC Complete Blood Count
CBCD Chronic Bullous Disease of Childhood (IgA linear dermatosis)
CBER Center for Biologics Evaluation and Research (US)
CBF (1) Cerebral Blood Flow; (2) Coronary Blood Flow
CBS Chronic Brain Syndrome
CC (1) Cervical Carcinoma; (2) Chief Complaint; (3) Coefficient of Correlation; (4) Common Cold; (5) Critical Condition; (6) Current Complaints
CCC Copyright Clearance Centre
CCF Congestive Cardiac Failure
CCI Collateral Circulation Index
CCL Centrocystic Lymphoma
CCM (1) Congestive Cardiomyopathy; (2) Commission Consultative Médicale (France)
CCr Creatinine Clearance
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)

CDM Clinical Data Management

CDP Clinical Development Plan

CDS Chemical Delivery System

CDSM Committee on Dental and Surgical Materials (UK)

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)

CEO Chief Executive Officer

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

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
CM&C Chemical, Manufacture & Control
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 Chief Medical Officer
CMR Client Meeting Report
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
COA Condition On Admission
COAD Chronic Obstructive Airway Disease
COBOL Common Business Oriented Language
COC Combined Oral Contraceptives
COLD Chronic Obstructive Lung Disease
COMPASS Computerised On-line Medicaid Pharmaceutical Analysis and Surveillance System
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
CP Cor Pulmonale, coeur pulmonaire
CPA Commonwealth Pharmaceutical Association
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
CRA Clinical Research Associate, Clinical Research Assistant
CRD (1) Chronic Renal Disease; (2) Chronic Respiratory Disease
CRE Clinical Research Executive
CRF (1) Case Record Form, Case Report Form, Clinical Record Form; (2) Corticotropin-Releasing Factor
CRIOC Consumer Organisations Research and Information Centre (Brussels)
CRM (1) Clinical Research Manager; (2) Committee on the Review of Medicines (UK advisory committee)
CRO Contract Research Organisation
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
CT (1) Clinical Trial; (2) Computer Tomography
CTA Clinical Trial Authorisation
CTC Clinical Trial Certificate
CTE Clinical Trial Exemption
CTFA Cosmetic, Toiletry and Fragrance Association
CTN Clinical Trial Notification
CTR Clinical Trial Report
CTS Clinical Trial Supplies
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

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
D.Ch. Doctor Chirurgiae
DDA Dangerous Drug Act (US)
DDD Defined Daily Dose
DDG Degenerative Disc Disease
DDX Doctor's and Dentist's Exemption scheme (from the need to obtain formal approval to do clinical trials in the UK)
DESI Drug Efficacy Study Implementation (FDA program)
DEA Drug Enforcement Agency (US)
DFS Disease Free Survival
DGSF (Italian Drugs Directorate)
DHHS Department of Health and Human Services (US)
DIA Drug Information Association
DIC Disseminated Intravascular Coagulation
DIN Deutsche Industrie-Norm (Deutsches Institut für Normung e.V.)
DJD Degenerative Joint Disease
DLP Data Lock-Point
DMAC Division of Drug Marketing, Advertising and Communications (FDA)
DMARD Disease Modifying Antirheumatic Drug
DMD (1) Disease Modifying Drug; (2) Duchenne Muscular Dystrophy
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 Drug Safety Monitoring
DTC Direct-To-Consumer
DTP (1) Diphtheria-Tetanus-Poliomyelitis; (2) Desk Top Publishing
DU Duodenal Ulcer
DUR Drug Utilisation Review
DVT Deep Vein Thrombosis

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
EBV Eppstein Barr Virus
EC (1) Ethics Committee; (2) European Community
ECG Electrocardiogram
ECHO Enteric Cytopathogenic Human Orphan (virus)
ECITC European Committee for Information Technology Testing and Certification
ECJ European Court of Justice
ECT Enteric Coated Tablet
ECU European Currency Unit
ED_{50} Median Effective Dose
EDL Essential Drug List
EDMA European Diagnostic Manufacturers Association
EDMF European Drug Master File
EDMUS European Database on Multiple Sclerosis
EDP Electronic Data Processing
EDV End Diastolic Volume
EEA European Economic Area
EEC European Economic Community
EEG Electroencephalogram
EIR Establishment Inspection Report
EFPIA European Federation of Pharmaceutical Industries Associations (Brussels)
EFTA European Free Trade Association
EGF Epidermal Growth Factor

EIA Exercise Induced Asthma
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 Evaluation Agency (EC)
EMEA European Medicines Evaluation Agency
EMG Electromyelogram
EOQ European Organization for Quality
EORTC European Organization for Research and Treatment of Cancer
EOTC European Organization for Testing and Certification
EP European Pharmacopoeia
EPA Environmental Protection Agency (US)
EPC (1) European Patent Convention; (2) European Pharmacopoeial Convention
EPhMRA European Pharmaceutical Market Research Association
EPS Earnings Per Share
ER Extended-Release
ERCP Endoscopic Retrograde Cholangio-Pancreatography
ESCOP European Scientific Corporation of Phytotherapy
ESCP European Society of Clinical Pharmacy
ESOP European Society for Pharmacovigilance
ESP Extrasensory Perception
ESR Erythrocyte Sedimentation Rate
ESRA European Society of Regulatory Affairs
et al. et alii (and coworkers)
EU European Union
EUCOMED European Confederation of Medical Device Associations
EVA Echelle Visuelle Analogique (visuel analogue scale)
EWL Evaporated Water Loss

F_1 Offspring from first generation
FÄPI Fachgesellschaft der Ärzte in der Pharmazeutischen Industrie (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)
FEFIM Fédération Française des Industries du Médicament
FI Fachinformation (German international physician's circular)
FIA Landelijke Vereniging van Farmaceutische Industrie-Artsen (Dutch association of physicians in the therapeutical industry)
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
FRCGP Fellow of the Royal College of General Practitioners
FRCP Fellow of the Royal College of Physicians
FTC Free Trade Commission (US)
FUO Fever of Unknown (Undetermined) Origin
FYI For Your Information

GALP Good Automated Laboratory 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 Gross Domestic Product
GFR Glomerular Filtration Rate
GH Growth Hormone
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
GMO Genetically Modified Organism
GMP Good Manufacturing Practice
GNP Gross National Product
GORD Gastro-Oesophageal Reflux Disease
GP General Practitioner
GPIA Generic Pharmaceutical Industry Association
GPM Gesellschaft für Pharmazeutische Medizin (Austria)
GPMSP Good Postmarketing Surveillance Practice (Japan)
GPS Good Pasture Syndrom
GRG Gesundheits-Reform-Gesetz (Germany)
GRP Good Regulatory Practice
GSG Gesundheit-Struktur-Gesetz (Germany)
GSL General Sale List medicine (UK)
GTT Glucose Tolerance Test
GU Gastric Ulcer
GVHD Graft Versus Host Disease

H_0 Null Hypothesis
H_1 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
HCL Hairy Cell Leukemia
HCMV Human Cytomegalovirus
HCV Hepatitis C Virus
HDP Hypertensive Disease in Pregnancy
HDRS Hamilton Depression Rating Scale
HHV Human Herpes Virus
HIV Human Immunodeficiency Virus
HLA Human Leucocyte Antigen
HMO Health Maintenance Organisation (US)
HNANB Hepatitis non A non B
HO (1) Heterotrophic Ossification; (2) House Officer, junior hospital doctor
HPI History of Present Illness
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
HSV Herpes Simplex Virus
HYE Healthy Year Equivalent
HZV Herpes Zoster Virus

IB Investigator's Brochure
IBD Inflammatory Bowel Disease
IBS Irritable Bowel Syndrome
IBW Ideal Body Weight
IC Inhibitory Concentration
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
ICGEB International Centre for Genetic Engineering and Biotechnology
ICH International Conference on Harmonisation (EC)
ICIDH International Classification of Impairments, Disabilities, and Handicaps
ICPC International Classification of Primary Care
ICU Intensive Care Unit
IDB Investigator's Drug Brochure
IDD Immunodeficency Disease
IDDM Insulin-Dependent Diabetes Mellitus
IDE Investigational Device Exemption
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
IKS Interkantonale Kontrollstelle für Heilmittel
IME Inborn Metabolic Error

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
IPH International Pharmacopoeia
IPMRG International Pharmaceutical Market Research Group
IPTSB International Programs and Technical Support Branch (FDA office for inspections)
IRB Institutional Review Board
IRDS Infant Respiratory Distress Syndrome
IS Infarct Size
ISBN International Standard Book Numbering
ISO International Organization for Standardization
IT Information Technology
ITQS Information Technology Quality System
ITT Intent-To-Treat
IU International Unit
IUCD Intra-Uterine Contraceptive Device
IUD Intra-Uterine Device
IVD In-Vitro Diagnostic
IVP Intravenous Pyelography

JPMA Japanese Pharmaceutical Manufacturers Association
JRA Juvenile Rheumatoid Arthritis

LAF Lymphocyte Activating Factor
LAN Local Area Network
LASA Linear Analogue Self Assessment
LD Lethal Dose
LDLo Lowest Lethal Dose
LFT Liver Function Test
LHA Local Health Authority
LMWH Low Molecular Weight Heparin
LPI Last Patient In
LPO Last Patient Out
LREC Local Research Ethics Committee
LRTI Lower Respiratory Tract Infection
LUTI Lower Urinary Tract Infection

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 Monoclonal Antibody
MADRS Montgomery–Asberg Depression Rating Scale
MAFS Mezinarodni Asociace Farmaceutickych Spolecnosti (Czech Association of Research Based Pharmaceutical Companies)
MaLAM Medical Lobby for Appropriate Marketing
MANOVA Multivariate Analysis of Variance
MB (1) Bachelor of Medicine; (2) Mängelbericht (report of the German BGA concerning deficiencies of a new drug application)
MBD Metastatic Bone Disease
MCA Medicines Control Agency (UK)
MCID Minimal Clinically Important Difference
MCT Multi-Centre Trial
MD (1) Maximum Acceptable Difference; (2) Medical Doctor
MDI Metered Dose Inhaler
MEC Minimum Effective Concentration
MED Minimum Effective Dosage
MEDIF (Pharmaceutical industries association in Denmark)
MEDLARS Medical Literature Analysis and Retrieval System (of the National Library of Medicine, Bethesda, Md., US)
MEFA (Danish domestic pharmaceutical industry association)
MI (1) Medicines Inspectorate (UK); (2) Myocardial Infarction
MIC Minimal Inhibitory Concentration
MID Minimal Infective Dose
MIF Migration Inhibition Factor
MIMS Monthly Index of Medical Specialities
MIS Management Information System
MLD Minimum Lethal Dose
MMR Measles/Mumps/Rubella
MNC Multi-National Company
MNLD Maximum Non-Lethal Dose
MOS Medical Outcome Study (quality of life instrument)
MPD Maximal Permissible Dose
MR Medical Representative
MRC Medical Research Council (UK)

MRD Maximum Repeatable Dose
MS Multiple Sclerosis
MSA Multi State Application
MSF Médecins Sans Frontières
MTC Minimum Toxic Concentration
MTD Maximal Tolerated Dose
MTR Monitor's Trip Report
MU Million Units
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)
NAPM National Association of Pharmaceutical Manufacturers (US)
NAS New Active Substance
NBAS New Biological Active Substance
NC No Change
NCC National Computing Centre (UK)
NCE New Chemical Entity
NCR No Carbon Required paper
ND Not Done
NDA New Drug Application
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)
NIDDM Non-Insulin Dependent Diabetes Mellitus
NIGMS National Institute of General Medical Sciences (US)
NIH National Institutes of Health (US)
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
NOEL No-Effect Level

NSAID Non-Steroidal Antiinflammatory Drug
NSR Non Significant Risk
NUG Necrotizing Ulcerative Gingivitis
NYHA New York Heart Association

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
OD (1) Once Daily; (2) Overdose; (3) Oculus Dextra (right eye)
OECD Organisation for Economic Cooperation and Development
OMB Office of Management and Budget
OPC One-Point-Cut (ampoules)
OPRR Office for Protection from Research Risks (US)
OS Oculus Sinistra (left eye)
OTC Over-The-Counter
OU Oculus Uterque (both eyes)

P Pharmacy Only
pa per annum
PAOD Peripheral Arterial Occlusive Disease
PAF Platelet Aggregating Factor
PAR Post-Approval Research
PBO Placebo
PC post cibum (after meals)
PCP Pneumocystis Carinii Pneumonia
PCSO Pharmaceutical Contract Support Organization
PD Progressive Disease
PDCA Plan Do Check Action-Cycle
PDE Phosphodiesterase
PDGF Platelet Derived Growth Factor
PDR Physicians Desk Reference
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
PI Parallel Import

PIC Pharmaceutical Inspection Convention
PID Pelvic Inflammatory Disease
PIH Pregnancy-Induced Hypertension
PIL Patient Information Leaflet
PILS Patient Information Leaflets
pINN proposed International Non-Proprietary Name
PL Product Licence, Parallel Import Product Licence
PLA Product Licence Application (US)
PMA Pharmaceutical Manufacturers' Association
PMO Post Menopausal Osteoporosis
PMP Proprietary Medical Product
PMS Post-Marketing Surveillance
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
PPRS Pharmaceutical Price Regulation Scheme
PR Partial Response
prn pro re nata (medication to be taken as needed, at discretion of the nurse)
PSA Prescription Sequence Analysis
PT Physical Therapy
PTCA Percutaneous Transluminal Coronary Angioplastie
PTO Patent and Trade Mark Office
PUD Peptic Ulcer Disease
PUO Pyrexia of Unknown Origin
PUVA Psoralen + Ultraviolet A
PVT Paroxysmal Ventricular Tachycardia

QA Quality Assurance
QALY Quality-Adjusted Life-Years
QAU Quality Assurance Unit
QC Quality Control
QID Quars In Die (four times daily)
QL Quality of Life
QoL Quality of Life

RA Rheumatoid Arthritis
RAD-AR Risk Assessment of Drugs – Analysis and Response
RAM Random Access Memory

RAPS Regulatory Affairs Professionals Society
RCGP Royal College of General Practitioners
RCC Renal Cell Carcinoma
RCT Randomised Controlled Clinical Trial
R&D Research and Development
RDA Recommended Daily Allowance
RDS Respiratory Distress Syndrome
REM Rapid Eye Movement
RHA Regional Health Authority
RIA Radioimmunoassay
ROC Return On Capital
ROM Read Only Memory
RSM Royal Society of Medicine
RSV Rous Sarcoma Virus
RTI (1) Respiratory Tract Infection; (2) Reverse Transcriptase Inhibitor

SAMM Safety Assessment of Marketed Medicines
S&A (urine) Sugar and Acetone test
SAC (1) Standardised Assessment of Causality; (2) Safety Assessment Candidate
SAS Statistical Analysis System
SBA Summary Basis of Approval
SBP Systolic Blood Pressure
SCI Science Citation Index
SD (1) Standard Deviation; (2) Stable Disease
SDA Standardised Decision Aids
SDI Spine Deformity Index
SDV Source Data Verification
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
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
SLE Systemic Lupus Erythematosus
SLS Selected List Scheme
SM Self-Medication

SMDA Safe Medical Devices Act
SME Small and Medium-sized Enterprises
SmPC Summary of Product Characteristics
SNIP Syndicat National de l'Industrie Pharmaceutique (French pharmaceutical industry association)
SNOMED Systematized Nomenclature of Medicine
SO Safety Officer
SOD Superoxide Dismutase
SOP Standard Operating Procedures
SPC (1) Summary of Product Characteristics; (2) Supplementary Protection Certificate
SPID Sum of Pain Intensity Differences
SPSS Statistical Package for the Social Sciences
SR (1) Sustained Release; (2) Significant Risk
SRS Spontaneous Report System
SSFA Società di Scienze Farmacologiche Applicate (Italian association of pharmaceutical physicians)
STD Sexually Transmitted Disease
STM Short Term Memory
SUR Safety Update Report
SVT Supraventricular Tachycardia

TAA Test Article Accountability (US)
TEN Toxic Epidermal Necrolysis
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
TNF Tumor Necrosis Factor
TOTPAR Total Area under the Pain Relief curve
TQM Total Quality Management
TRIC Trachoma and Inclusion Conjunctivitis
TRIPS Trade-Related Intellectual Property (talks)
TSCA Toxic Substance Control Act (US)

UDS Unscheduled DNA repair Synthesis
UNDP United Nations Development Programme
UNICEF United Nations International Children's Emergency Fund

UNIDO United Nations Industrial Development Organization
URTI Upper Respiratory Tract Infection
USAN United States Adopted Names
USP United States Pharmacopoeia
USPDI United States Pharmacopoeia Dispensing Information
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
VDP Visual Display Unit
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)

Selected bibliography

CIOMS

International reporting of adverse drug reactions. Final report of CIOMS working group; Council for International Organizations of Medical Sciences, Geneva, 1990.

International reporting of periodic drug-safety update summaries. Final report of CIOMS working group II; Council for International Organizations of Medical Sciences, Geneva, 1992.

European Community (EC)

The rules governing medicinal products in the European Community, vol. I: The rules governing medicinal products for human use in the European Community; revised ed./ September 1991; catalogue no. CO-71-91-631-EN-C; Brussels, Luxembourg, 1991.

The rules governing medicinal products in the European Community, vol. II: Notice to applicants for marketing authorizations for medicinal products for human use in the member states of the European Community; catalogue no. CB-55-89-293-EN-C; Brussels, Luxembourg, 1989.

The rules governing medicinal products in the European Community, vol. III: Guidelines on the quality, safety and efficacy of medicinal products for human use; addendum 1990; catalogue no. CB-59-90-936-EN-C; Brussels, Luxembourg, 1990.

The rules governing medicinal products in the European Community, vol. IV: Guide to good manufacturing practice for medicinal products; catalogue no. CB-55-89-722-EN-C; Brussels, Luxembourg, 1989.

The rules governing medicinal products for veterinary use in the European Community, vol. V: Veterinary medicinal products; catalogue no. CB-55-89-972-EN-C; Brussels, Luxembourg, 1989.

Federal Republic of Germany

IFPMA code of pharmaceutical marketing practices; Bundesverband der pharmazeutischen Industrie e.V. Ed. Cantor, Aulendorf, 1989.

Nordic countries

Good clinical trial practice; NLN Publication no. 28; December 1989.

United Kingdom

Guidelines on good clinical research practice. The Association of the British Pharmaceutical Industry (ABPI), London, March 1988.

Code of practice for the pharmaceutical industry, 8th ed. The Association of the British Pharmaceutical Industry (ABPI), London, January 1993.

Prescription medicines code of practice authority: constitution and procedure. The Association of the British Pharmaceutical Industry (ABPI), London, January 1993.

Guidelines for medical experiments in non-patient human volunteers. The Association of the British Pharmaceutical Industry (ABPI), London, March 1988.

Guidelines on post-marketing surveillance. Joint committee of ABPI, BMA, CSM, and RCGP. BMJ 296: 399–400 (1988).

United States of America

Code of Federal Regulations, published by the Office of the Federal Register National Archives and Records Administration:
21 CFR part 50 – Protection of human subjects;
21 CFR part 56 – Institutional review boards;
21 CFR part 312 – Investigational new drug application;
21 CFR part 314 – Applications for FDA approval to market a new drug or an antibiotic drug.

FDA compliance program guidance manual; Bernan Associates, Lanham, Md.:
Clinical Investigators (CP 7348.811), 1991;
Sponsors, contract research organizations and monitors (CP 7348.810), 1991;
Institutional review boards (CP 7348.808), 1991;
In vivo bioequivalence (CP 7348.001), 1991.

Guideline for the format and content of the clinical and statistical sections of new drug applications. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, Md., July 1988.

Guideline for the format and content of the human pharmacokinetics and bioavailability section of an applications. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drugs and Biologics, Rockville, Md., February 1987.

Guideline for postmarketing reporting of adverse drug experiences. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, Md., March 1992.

WHO

Adverse reaction dictionary. WHO Collaborating Centre for International Drug Monitoring, Uppsala (regularly updated).

Drug dictionary. WHO Collaborating Centre for International Drug Monitoring, Uppsala (regularly updated).

Guidelines for good clinical research practice (GCP) for trials on pharmaceutical products, draft September 1992. WHO Division of Drug Management and Policies, Geneva, 1992.

Guidelines for ATC classification. WHO Collaborating Centre for Drug Statistics Methodology. WHO Regional Office for Europe, Oslo (annually updated).

Handbook for reporting results of cancer treatment; WHO offset publication no. 48. WHO, Geneva, 1979.

International statistical classification of diseases and related health problems (ICD-10), 10th revision. WHO, Geneva, 1992.

International classification of diseases for oncology (ICD-O). WHO, Geneva, 1976.

Important addresses

National bodies and organisations

Argentina

AMAIFA
Asociacion de Médicos Asesores de la Industria Farmacéutica Argentina
Delegate to IFAPP: Dr. Luis Collia (Secretary of AMAIFA)
Laboratorios CASASCO, Carabobo 22, 1406 Buenos Aires, Argentina
tel: 90054-1-632 5091/93, fax: 90054-1-633 1173

Austria

Bundesministerium für Gesundheit, Sport und Konsumentenschutz, Sektion II – Gesundheitswesen
(Ministry of Health)
Radetzkystrasse 2, A-1030 Wien, Austria
tel: + 43-1-711 72-0, fax: + 43-1-712 09 23

Bundesstaatliches Serumprüfungsinstitut/ Bundesstaatliche Impfgewinnungsanstalt
(Federal institute for sera, vaccines and allergens)
Possingergasse 38, A-1160 Wien, Austria
tel: + 43-1-492 00 70-0

FCI
Fachverband der Chemischen Industrie,
Gruppe Pharmazeutika (association representing the pharmaceutical industry in Austria)
Wiedner Hauptstrasse 63, Postfach 325, A-1045 Wien, Austria
tel: + 43-1-501050/3373, fax: + 43-1-50206 280

GPM
Gesellschaft für Pharmazeutische Medizin e.V.
Delegate to IFAPP: Dr. med. Dr. phil. Gerhard Nahler (President of GPM),
CIS Clinical Investigation Support GmbH. & Co KG
Kaiserstrasse 43, A-1070 Wien, Austria
tel: +43-1-52 40 15, fax: +43-1-52 40 17

IGEPHA
(represents the OTC industry in Austria)
Hütteldorferstrasse 175, A-1140 Wien, Austria
tel: + 43-1-94 95 12

PHARMIG
(represents the pharmaceutical industry in Austria)
Zieglergasse 5, A-1072 Wien, Austria
tel: + 43-1-523 29 51, fax: + 43-1-523 29 519

Australia

APPA
Australian Pharmaceutical Physicians Association
Contact for IFAPP: Dr. Susan J. Alder (Secretary of APPA)
Abbott Australasia Pty. Ltd.
P.O. Box 101, Cronulia, NSW 2230, Australia

Department of Health, Housing and Community Services
Central Office: Furzer St, GPO 9848, Phillip, Canberra,
ACT 2601, Australia
tel: + 06-16-289 1555, fax: + 06-16-281 6946

Belgium

ABEMIP/BEVAFI
Association Belge des Médecins de l'Industrie Pharmaceutique/
Belgische Vereniging der Artsen van de Farmaceutische
Industrie
11, avenue des Hannetons, B-1170 Bruxelles, Belgium
Delegate to IFAPP: Dr. Herman F.J. Lahon, Direction médicale, UCB Secteur Pharmaceutique
Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium
tel: + 32-2-386 25 30, fax: + 32-2-384 55 29

AGIM
Association Générale de l'Industrie du Médicament
49 place Marie Louise, B-1049 Bruxelles, Belgium
tel: +32-2-238 9711, fax: +32-2-231 1164

Ministère de la Santé Publique, Inspection Générale de la Pharmacie / Ministerie van Volksgezondheit, Farmaceutische Inspektie
Cité Administrative, Quartier Vésale, B-1010 Bruxelles, Belgium
tel: +32-2-210 4893, fax: + 32-2-220 4880, telex: + 25768 MVGSPF B

Brazil

ABMAIF
Associção Brasileirea de Médico Assessores da Indústria Farmacêutica
rua Pamplona 788, 3° andar, sala 32, Sao Paulo SP,
Brazil 01405-001
tel: + 55-11-251 2119
Delegate to IFAPP: Dr. Dagoberto C. Brandao (President of ABMAIF), Hoechst do Brazil
8° andar, sala 843, av. Nacoes Unidas, 18001, Sao Paulo SP, Brazil 04795-900
tel: + 55 -1-525 7804, fax: + 55-11-525 7878

Canada

ACPP/ACMIP
Association of Canadian Pharmaceutical Physicians / Assocation Canadienne des Médecins de l'Industrie Pharmaceutique
Contact for IFAPP: Mr. Anthony K. Knill, PMAC-ACIM
302-1111, Prince of Wales Drive, Ottawa, Ontario K2C 3T2, Canada
tel: + 16-13-727 13 80, fax: + 16-13-727 14 07

Department of National Health and Welfare
Jeanne Mance Bldg., Ottawa, Ontario K1A OK9, Canada
tel: + 16-13-957 2991

Department of National Health and Welfare
Medical Services Branch
Tulleys Pasture, Ottawa, Ontario K1A OL3, Canada

Czechia

Ministry of Health of the Czech Republic
Palackého nám 4, 12801 Praha 2, Czechia
tel.: + 42-2-24971111, fax: + 42-2-290092

SÚKL State Institute for Drug Control
Committee for New Drugs
Srobárova 48, 10041 Praha 10 - Vinohrady, Czechia
tel: + 42-2-290772, fax: + 42-2-290772

Denmark

BFID
Brancheforeningen af Farmaceutiske Industrivirksomheder i Danmark
(association of pharmaceutical industries in Denmark)
Director: Mr. Jorgen Reument
Taastrupgaardsvej 30, DK-2630 Taastrup, Denmark
tel: + 45-43 710 199, fax: + 45-43 710 199

FLE
Foreningen af Laeger i Erhvervslivet
(Danish Association of Physicians in Private Employment)
Delegate to IFAPP: Dr. Kirsten Roenborg, Ciba-Geigy 7s, Lyngbyvej 172, DK-2100 Copenhagen, Denmark
tel: + 45-392 914 22, fax: + 45-392 914 84

MEDIF
Pharmaceutical Industries Association in Denmark
(represents companies marketing medicines in Denmark)
Strødamvej 50 A, DK-2100 Copenhagen, Denmark
tel: + 45-39 270 910, fax: + 45-39 270 911

MEFA
Foreningen af Danske Medicinfabriken
(Association of the Danish Pharmaceutical Industry)
Strodamvej 50A, DK-2100 Copenhagen, Denmark
tel: + 45-39 270 088, fax: + 45-39 270 050

Sundhedsstyrelsen, Laegemiddelafdelingen (Ministry of Health)
Frederikssundsvej 378, DK-2700 Brønshøj, Denmark
tel: + 45-29 436 77, fax + 45-28 470 77, telex: 35333 IPHARM DK

Finland

Finnish National Agency for Medicines
Pharmaceutical and pharmocological departments
Mannerheimintie 166, P.O. Box 55, SF-00301 Helsinki, Finland
tel: + 358-0-47441, fax: + 358-0-4744525

FPIF
The Finnish Pharmaceutical Industry Federation
(represents domestic and non-Finnish, pharmaceutical firms within Finland)

Iso Roobertinkatu 4–6A, P.O. Box 320, SF-00121 Helsinki, Finland
tel: + 358-0-641 124, fax: + 358-0-62 706

SuII/fiAPP
Suomen Lääketeollisuuden Lääkärit
(Finnish Association of Pharmaceutical Physicians)
Delegate to IFAPP: Dr. Pentti Timonen,
Orion Farmos Pharmaceuticals, Farmos Research,
Clinical Research Development
P.O. Box. 425, SF-20101 Turku, Finland

France

AFNOR
Association Francaise de Normalisation
Tour Europe, F-92080 Paris La Défense Cedex 7, France

AMIP
Association des Médecins de l'Industrie Pharmaceutique
(IFAPP Member)
Secretariat permanent de l'AMIP
83, av. André Morizet, F-92100 Boulogne, France
tel: + 33-1-499 138 56, fax: + 33-1-499 132 96

APGI
Association de Pharmacie Galénique Industrielle
(pharmaceutical technology, pharmaceutics, biopharmacy, dermopharmacy)
rue J.B. Clément, F-92296 Chatenay-Malabry, Cedex, France
tel: + 33-1-46 60 25 10, 46 83 55 81, fax: + 33-1-46 83 53 08

FEFIM
Fédération Française des Industries du Médicament
25 rue de Montevideo, F-75116 Paris, France
tel: + 33-1-45 03 88 88, fax: + 33-1-45 04 47 71

Ministere de la Solidarite, de la Santé et de la Protection Sociale
Diréction de la Pharmacie et du Médicament
1, place de Fontenoy, F-75700 Paris, France
tel: + 33-1-40 56 60 00, fax: + 33-1-405 65 355,
telex: 250011 SANTSEC F

SNIP
Syndicat National de l'Industrie Pharmaceutique
88, rue de la Faisanderie, F-75007 Paris 16, France
tel: + 33-1-45 03 88 70, fax: + 33-1-45 03 34 25

Federal Republic of Germany

BAH
Bundesfachverband der Arzneimittel-Hersteller e.V.
Ubierstraße 73, D-53173 Bonn, Germany
tel: + 49-228-361 026, fax: + 49-228-355 861

BPI
Bundesverband der Pharmazeutischen Industrie e.V.
Postfach 110251, Karlstrasse 21, D-60329 Frankfurt/M., Germany
tel: + 49-69-740 477, fax: + 49-69-237 813

Deutsches Institut für Normung e.V.
Postfach 1107, Burggrafenstrasse 4–10, D-10787 Berlin, Germany
tel: + 49-30-26 010

FÄPI
Fachgesellschaft der Ärzte in der Pharmazeutischen Industrie
Delegate to IFAPP: Dr. Volker Gladigau,
Medical Department, Boehringer Ingelheim
Postfach 200, D-55216 Ingelheim am Rhein, Germany
tel: + 49-6-132 772 041, fax: + 49-6-132 773 818

Institut für Arzneimittel des Bundesgesundheitsamtes
Seestrasse 10, D-13353 Berlin, Germany
tel: + 49-30-450 22 03, fax: + 49-30-450 22 07,
telex: (2627) (17) 308062 BGESA D

Paul Ehrlich Institut, Bundesamt für Sera und Impfstoffe
(sera, vaccines and allergens)
Postfach 700810, Paul Ehrlich Strasse 42–44,
D-60558 Frankfurt/M., Germany
tel: + 49-69-63 60 16, fax: + 49-69-63 44 02, telex: 69907 16

Greece

EOF
(National Drug Oranisation)
284 Messogion Av., Holargos, GR-15562 Athinai, Greece
tel: + 30-1-654 5531, fax: + 30-1-654 5535

IFAPP Contact: Dr. A.E. Georgiadis, Ciba-Geigy Hellas
P.O. Box 8282, GR-10010 Athinai, Greece
tel: + 30-1-666 66 12

SPEE
(Association of Pharmaceutical Companies in Greece; represents manufacturers of ethical, pharmaceuticals in Greece)
Contact: Emil Koutsoff
1517 Tsoha Street, GR-11521 Athinai, Greece
tel: + 30-1-644 72 71, 643 01 04, fax: + 30-1-641 1463

Hungary

Hungarian Pharmaceutical Manufacturers Association
Amerikai út 96, H-1145 Budapest, Hungary
tel: + 36-1-251 3677, fax: + 36-1-251 3337

Nepjoleti Miniszterium (Ministry of Public Welfare)
Arany J.o. 6–8, H-1051 Budapest, Hungary
tel: + 36-1-13231, fax: + 36-1-1328 750

NIP (National Institute of Pharmacy)
Zrinyi u. 3, H-1051 Budapest, Hungary
tel: + 36-1-117-0, fax: + 36-1-118-1167

India

AMAPI (Association of Medical Advisers in the Pharmaceutical Industry (India))
Delegate to IFAPP: Dr. Kiran V. Marthak, Medical Director, German Remedies Ltd.
Shivsagar Estate, Block A, Dr. Annie Besant Road, Worli, Bombay 400018, India
tel: + 91-22-493 5528, fax: + 91-22-492 6457

Indonesia

IPPA
The Indonesian Pharmaceutical Physicians Association
Delegate to IFAPP: Dr. Theo Palit, Director Medical Affairs, Glaxo Indonesia
Jl. Pulobuaran Raya Kav III DD/2,3,4,
Kawasan Industri Pulogadung, Jakarta 13930, Indonesia
tel: + 62-21-4603292, fax: + 62-21-4603330

Ireland

FICI
Federation of Irish Chemical Industries
(represents the chemical and pharmaceutical industry in Ireland for manufacturers of ethical and OTC medicines)
Franklin House, 140 Pembroke Road, Dublin 4, Ireland
tel: + 353-1-603 350/603 661, fax: + 353-1-686 672

National Drugs Advisory Board
63-64 Adelaide Road, Dublin 2, Ireland
tel: + 353-1-764 971, fax: + 353-1-767 836, telex: + 90542

Israel

IFAPP Contact: Dr. Arnon Tamir, Medical Director,
ABIC Ltd., Pharma & Chem. Industries
Industrial Zone, P.O. Box 8077, Kiryat Nordau, Netanya, Israel
tel: + 972-53-639777, fax: + 972-53-54221/54129

Italy

Assosalute
(represents OTC companies in Italy)
Via Accademia 33, I-20131 Milano, Italy
tel: + 39-2-26810251, fax: + 39-2-26 81 03 48

Farmindustria
Associazione Nazionale dell'Industria Farmaceutica
(represents domestic and foreign pharmaceutical firms in Italy)
Piazza di Pietra 34, I-00186 Roma, Italy
tel: + 39-6-675 801, fax: + 39-6-786 494

Ministeria della Sanita
Servizio Farmaceutico
Viale della Civitta Romana 7, I-00144 Roma, Italy
tel: + 39-6-592 5863, fax: + 39-6-592 5824,
telex: + 625205 MINSAN I

SSFA
Società di Scienze Farmacologiche Applicate
P.O. Box 10741 I-20110 Milano, Italy
fax: + 39-2-29520 179

Delegate to IFAPP: Dr. Luciano M. Fucella, Tecnofarmaci
Via Enrico Nöe, 23, I-20133 Milano, Italy
tel: + 39-2-706 34 20, fax: + 39-2-706 352 53

Japan

European Business Community
(represents pharmaceutical companies of European origin)
c/o Hoechst Japan
10-16 Akasaka 8-chome, Minato-ku, Tokyo 107, Japan
tel: + 81-3-34 79 7524, fax: + 81-3-34 79 5157

Federation of Pharmaceutical Manufacturers Associations of Japan
(represents ten national industry groups including the JPMA and regional bodies)
Tokyo Yakugyo Kaikan, 2-1-5 Nihonbashi Hon-cho, Chuo-ku, Tokyo 103, Japan
tel: + 81-3-3270 0581

JAMDI
Japanese Association of Medical Doctors in Drug Industries
Delegate to IFAPP: Dr. Yukata Nojima,
Otsuka Pharmaceutical Co. Ltd.
2-2 Kanda Tsukasa-cho, Chiyoda-ku, Tokyo 101, Japan
tel: + 81-3-32 576546, fax: + 81-3-32 576566

JAPMM
Japanese Association of Proprietary Medicine Manufacturers
Eiraku Building, 1-8-9 Nihonbashi Kakigara-cho, Chuo-ku, Tokyo 103, Japan
tel: + 81-3-3661 6155

JPMA
Japanese Pharmaceutical Manufacturers Association
Torii Nihonbashi Building, 3-4-1 Nihonbashi Hon-cho, Chuo-ku, Tokyo 103, Japan
tel: + 81-3-3241 0326, fax: + 81-3-3242 1767

Koseisho (Ministry of Health and Welfare)
1-2-2, Kasumigaseki, 1 Chome, Chiyoda-ku, Tokyo 100, Japan
tel: + 81-3-35 03 1711

National Institute of Health
2-10-35 Kami-Osaki, Shinagawa-ku, Tokyo 141, Japan
tel: + 81-3-3444 2181

PMA
Pharmaceutical Manufacturers Association (US)
(represents PMA member companies in Japan)
Tosaka Building, 1-23 Kanda Nishiki-cho, Chiyoda-ku,
Tokyo 101, Japan
tel: + 81-3-3294 6533

Luxembourg

Ministère de la Santé
Direction de la Santé,
Division de la Pharmacie et des Médicaments
10 rue C.M. Spoo, L-2546 Luxembourg
tel: + 432-408 01, fax: + 432-484 903,
telex: + 2546 SANTE LU

Mexico

AMEIFAC
Asociación de Médicos Especialistas en la Industria
Farmacéutica, A.C., Canifarma
av. Cuauhtémoc 1481, 03310 Mexico DF, Mexico
tel: + 52-5-688 9885, fax: + 52-5-604 9808
Delegate to IFAPP: Dr. Victor Fortuno Cordova
(President of AMEIFAC), Medical Director,
Latin America Division, ICN Farmaceutica, S.A. de C.V.
Calz. Ermita Iztapalapa, 436, Col. Mexicaltzingo,
09080 Mexico DF, Mexico
tel: + 52-5-811 396, fax: + 52-5-814 938

The Netherlands

College ter beoordeling van geneesmiddelen
S.W. Churchilliaan 362, P.O. Box 5811, NL-2280 HV Rijswijk
(ZH), The Netherlands
tel: + 31-70-40 70 08, fax: + 31-70-40 50 48,
telex: + 1680 WVCRW NL

European Federation of Pharmaceutical Sciences
FIP Congress Department
Alexanderstraat 11, NL-2514 JL The Hague, The Netherlands
tel: + 31-70-36 31 925, fax: + 31-70-36 59 047

FIA
Landelijke Vereniging van Farmaceutische Industrie-Artsen
Secretariaat F.I.A.: Mrs. C. van Galen
Kamgras 10, NL-3648 HM Wilnis, The Netherlands
tel: + 31-2979 81121, fax: + 31-2979 41401
Delegate to IFAPP:
Dr. J.M.A. Penders,
Pfizer B.V., Pharmaceuticals Division
P.O. Box 37, NL-2900 AA Capelle a/d Ijssel, The Netherlands
tel: + 31-10 406 4200, fax: + 31-10 406 4299

Nefarma
Nederlandse Vereniging van de Innoverende Farmaceutische Industrie
(represents prescription manufacturers)
Pallas Athenedreef 31, Postbus 9193, NL-3506 GD Utrecht, The Netherlands
tel: + 31-30-621 444, fax: + 31-30-614 554

New Zealand

Health Department
P.O.Box 5012, Wellington, New Zealand
fax: + 64-4-496 2340
Delegate to IFAPP: Dr. Gavin Frost, Medical Affairs,
3M-Riker Lab. Ltd.
C.P.O. Box 2201, Auckland, New Zealand
tel: + 64-9-444 5289, fax: + 64-9-444 5770

Norway

NOMI
Norges Medisinalindustris Felleskontor
(represents Norwegian drug manufacturers)
P.O. Box 847 Sentrum, N-0104 Oslo, Norway
tel: + 47-2-241 76 75, fax: + 47-2-241 76 76

NO-RE-FARM
(represents the interests of 38 foreign pharmaceutical firms manufacturing in Norway)
P.O. Box 847, N-0105 Oslo, Norway
tel: + 47-2-2 41 76 86, fax: + 47-2-2 41 76 85

Norwegian Association of Physicians in the Pharmaceutical Industry
Delegate to IFAPP: Dr. Hogne Vik, Nycomed A/S
P.O. Box 4220 Torshov, N-0401 Oslo 4, Norway
tel: + 47-2-89 1010, fax: + 47-2-89 1212

Philippines

Philippine College of Pharmaceutical Medicine
Unit 502, One Corp. Plaza Cond., 845 Pasay Road,
Makati M.M., Philippines
tel: + 63-2 813 3539
Delegate to IFAPP: Dr. Cecilia Arellano-Isaac, Office of the Asst. Vice President, Medical Affairs, United Laboratories, Inc. 66, United St., 1501 Mandaluyong, Metro Manila, Philippines
tel: + 63-2-631 8501, fax: + 63-2-633 2626

Poland

Ministerstvo Zdrowia
(Ministry of Public Health)
ul. Miodowa 15, PL-00923 Warszawa, Poland
tel: + 48-22-31 34 41-49, fax: + 48-22-635 92 45

Portugal

AMPIF
Associação dos Médicos Portugueses da Industria Farmacéutica
av. Gago Coutinho 151, P-1700 Lisboa, Portugal
Delegate to IFAPP: Dr. Miguel Vigeant Gomes,
Janssen Farmacéutica
Campo Grande, 28, 1° D, P-1700 Lisboa, Portugal
tel: + 351-1-79 79 643, fax: + 351-1-79 70 150

APIFARMA
(represents domestic and foreign pharmaceutical firms)
Avenida duque de Avilla 95-2°, P-1000 Lisboa, Portugal
tel: + 351-1-31 51 24 8, fax: + 351-1-543 52 75

Ministero da Saude
Direçao Geral dos Assuntos Farmaceuticos
Av. Estados Unidos de America, 37, P-1700 Lisboa, Portugal
tel: + 351-1-80 41 31, fax: + 351-1-88 03 31, telex: + 15655 MAS P

Russia

Ministry of Health of the Russian Federation
Rakhmanovski BJR 3, Moskwa 101 401, Russia
tel: + 7-095-411 407, fax: + 7-095-200 0212

Slovakia

Ministerstvo Zdravotnitcva
(Ministry of Health of the Slovakian Republic)
Foreign Department
Spitalska 6, SLK-81325 Bratislava, Slovakia
tel: + 42-7-300, fax: + 42-7-334912 (Foreign Dept.)

State Institute for the Control of Drugs
Kvetná 11, SLK-82508 Bratislava 26, Slovakia
tel: + 42-7-63169, -211925, -211860, fax: + 42-7-213160

Slovenia

Slovenian OTC Group
Lek dd Pharmaceutical and Chemical Company
Verovskova 57, PO Box 81, SLO-61107 Ljubljana, Slovenia
tel: + 38-61-182161, fax: + 38-61-183517

South Africa

SAPIMAG
South African Pharmaceutical Industry Medical
Advisers Group
IFAPP Contact: Mrs. Joy Eckard, Ciba Geigy Pty. Ltd.
72/74 Steel Road, Spartan-Kempton Park 1620,
Republic of South Africa

Spain

ANEPP
Associacion Nacional de Especialidades Farmacéuticas
Publicitarias
Juan Alvarez de Mendizabal 47, bajo A, E-28008 Madrid, Spain
tel: + 34-1-559 74 94, fax: + 34-1-541 50 71

Asociación de Medicos de la Industria Farmacéutica Española
Villanueva, 11, 3°, E-28001 Madrid, Spain

Delegate to IFAPP: Dr. Julián Ruiz-Ferrán,
Management Pharmaceutical Consultant
Paseo de la Castellana, 153, E-28046 Madrid, Spain
tel:/fax: + 34-1-579 1117

Farmaindustria
(represents Spanish and non-Spanish pharmaceutical firms)
Fray Juan Gil 5, E-28046 Madrid, Spain
tel: + 34-1457 8351, fax: + 34-1-457 2225

Ministereo de Sanidad y Consumo, Direccion general de Farmacia y Productos sanitarios
Paseo del Prado, 18–20, E-28014 Madrid, Spain
tel: + 34-1-467 34 28, fax: + 34-1-420 10 42
telex: + 22608 MSASS

Sweden

LIF
Läkemedelsindustriforeningen
(represents Swedish pharmaceutical firms)

RUFI
(represents non-Swedish pharmaceutical firms within Sweden)
Nybrogatan11 3tr, P.O. Box 5522, S-114 85 Stockholm, Sweden
tel: + 46-8-670 3700, fax: + 46-8-663 8680

LL
Läkemedelsindustrins Läkarförening
(Swedish Association of Physicians in the Pharmaceutical Industry)
Delegate to IFAPP: Prof. Anders Rosén,
Bristol-Myers Squibb Scandinavia
P.O. Box 15200, S-16115 Bromma, Sweden
tel: + 46-8-70 47 100, fax: + 46-8-70 48 931

Switzerland

ASSGP
Association Suisse des Fabricants de Spécialités Grand Public
(represents OTC companies in Switzerland)
Case Postale 34, CH-1196 Gland, Switzerland
tel: + 41-22-364 68 39, fax: + 41-22-364 68 33

Bundesamt für Gesundheitswesen
Pharmacy Dept. (General Welfare Office)
Postfach, CH-3001 Bern, Switzerland
tel: + 41-31-911 00 51, fax: + 41-31-911 03 19

IKS
Interkantonale Kontrollstelle für Heilmittel
Erlachstrasse 8, CH-3000 Bern 9, Switzerland
fax: + 41-31-302 06 54

Interpharma
(association of the three big Swiss firms)
Petersgraben 35, P.O. Box, CH-4003 Basel, Switzerland
tel: + 41-61-261 44 86, fax: + 41-61-261 47 34

Pharma Information
Petersgraben 35, CH-4003 Basel, Switzerland
tel: + 41-61-261 07 07, fax: + 41-61-261 38 61

SSCI/SGCI
Swiss Society of Chemical Industries
(represents the chemical industry)
Nordstrasse 15, Postfach 328, CH-8035 Zürich, Switzerland
tel: + 41-1-363 1030, fax: + 41-1-363 1018

United Kingdom

ABPI
Association of the British Pharmaceutical Industry
(represents UK prescription medicine manufacturers)
Information Officer: Gail Turner,
12 Whitehall, London SW1A 2DY, United Kingdom
tel: + 44-71-930 3477, fax: + 44-71-930 3290

BGMA
British Generic Manufacturers Association
98 Bicester Road, Oakley HP18 9QG, United Kingdom
tel: + 44-844 237 680, fax: + 44-844 238 477

BrAPP
British Association of Pharmaceutical Physicians
c/o Royal Society of Medicine,
1, Wimpole Street, London W1M 8AE, United Kingdom
tel: + 44-71-491 86 10, fax: + 44-71-499 24 05

Delegate to IFAPP: Prof. Peter Stonier, Medical Director,
Hoechst UK Ltd.
50, Salisbury Road, Hounslow Middlesex TW4 6JH,
United Kingdom
tel: + 44-81-75 43 255, fax: + 44-81-56 94 834

BPG
British Pharma Group Ltd.
c/o Glaxo Pharmaceuticals UK Ltd.,
Stockley Park West, Uxbridge UB11 1BU, United Kingdom
tel: + 44-81-990 2175, fax: + 44-81-990 4352

BSI
British Standards Institution
2 Park Street, London W1A 2BS, United Kingdom

Medicines Control Agency
Department of Health
Market Towers, 1 Nine Elms Lane, Vauxhall,
London SW8 5NQ, United Kingdom
tel: + 44-71-273 000

Department of Health, Medicines Division
Britannia House, 7 Trinity Street, London SE1 1DA,
United Kingdom
tel: + 44-71-407 55 22

OHE
Office of Health Economics
12 Whitehall, London SW1A 2DY, United Kingdom
tel: + 44-71-930 9203, fax: + 44-71-976 1962

United States of America

Government offices

Centers for Disease Control
Office of Public Affairs
1600 Clifton Road NE, Building 1-2067, D-25,
Atlanta GA 30333, USA
tel: + 1-404-639 3286, fax: + 1-404-639 1623

Department of Health and Human Services
200 Independence Avenue SW, Washington, DC 20201, USA
tel: + 1-202-690 6343, fax: + 1-202-690 6247

Food and Drug Administration
20 Constitution Avenue NW, Washington, DC 20418, USA
tel: + 1-202-334 2138, fax: + 1-202-334 2158

Office of Public Affairs
5600 Fishers Lane, Room 15-05, Rockville, MD 20857, USA
tel: + 1-301-443 1130, fax: + 1-301-227 6004

Freedom of Information Services Inc.
Office of Public Affairs
12315 Wilkins Avenue, Rockville, MD 20852-1877, USA
tel: + 1-301-881-0410, fax: + 1-301-881-0415

National Academy of Sciences
Institute of Medicine
National Research Council
2101 Constitution Avenue NW, Washington, DC 20418, USA
tel: + 1-202-334 2000

National Center for Health Statistics
6525 Belcrest Road, Hyattsville, MD 20782, USA
tel: + 1-301-436 7551

National Institutes of Health
Building 1, Room 344, Bethesda, MD 20892, USA
tel: + 1-301-496 5787

Office of the Inspector General
Wibur J. Cohen Building, Room 5250,
330 Independence Avenue SW, Washington, DC 20201, USA
tel: + 1-202-619 3148

The Patent and Trademark Office
US Department of Commerce
2011 Crystal Drive, CPK-2 Suite 2088, Arlington, VA 22202, USA
tel/fax: + 1-703-305 8341

Public Health Service
Hubert H. Humphrey Building,
200 Independence Avenue SW, Washington, DC 20201, USA
tel: + 1-202-245 7694

US Consumer Product Safety Commission
5401 Westbard Avenue, Bethesda, MD 20816, USA
tel: + 1-301-504 0580, fax: + 1-301-504 0399

Trade and professional associations

Generic Pharmaceutical Industry Association
200 Madison Avenue, Suite 2404, New York, NY 10016 USA
tel: + 1-212-683 1881, fax: + 1-212-213 2105

The Gerontological Society of America
1275 K Street NW, Suite 350, Washington, DC 20005-4006, USA
tel: + 1-202-842 1275

National Association of Manufacturers
1331 Pennsylvania Avenue NW, Suite 1500 North,
Washington, DC 20004, USA
tel: + 1-202-637 3087

National Association of Pharmaceutical Manufacturers
747 Third Avenue, New York, NY 10017, USA
tel: + 1-212-838 3720, fax: + 1-212-752 6832

National Institute of Standards and Technology
Quince Orchard and Clopper Roads, Gaithersburg, MD 20899,
USA
tel: + 1-301-975 2000

National Pharmaceutical Association
2300 Fourth Street NW, Washington, DC 20059, USA
tel: + 1-202-328 9229

Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue NW, Suite 1200,
Washington, DC 20036, USA
tel: + 1-202-429 9260, fax: + 1-202-223 6835

Parenteral Drug Association
7500 Old Georgetown Road, Suite 920, Bethesda, MD 20814,
USA
tel: + 1-301-986 0293, fax + 1-301-986 0296

Pharmaceutical Advertising Council
110 East 42d Street, Suite 1310, New York, NY 10017, USA
tel: + 1-212-370 1701, fax: + 1-212-599 8492

Pharmaceutical Manufacturers Association
1100 15th Street NW, Washington, DC 20005, USA
tel: + 1-202-835 3460, fax: + 1-202-835 3414

Regulatory Affairs Professional Society
12300 Twinbrook Parkway, Suite 630, Rockville, MD 20852, USA
tel: + 1-301-770 2920, fax: + 1-301-770 2924

US Pharmacopeial Convention
12601 Twinbrook Parkway, Rockville, MD 20852, USA
tel: + 1-301-881 0666, fax: + 1-301-816 8247

International bodies and societies

AESGP
European Proprietary Medicines Manufacturers Association
7 avenue de Tervuren, Box 4, B-1040 Bruxelles, Belgium
tel: + 32-2-7355130, fax: + 32-2-735 5222

BEUC
Bureau Européen des Unions de Consommateurs
(represents national consumer organizations in most European countries)
36 avenue de Tervuren, Box 4, B-1040 Bruxelles, Belgium
tel: + 32-2-735 3110, fax: + 32-2-735 7455

CEFIC
European Chemical Industry Council
(represents the chemical industry at the EC level)
4 avenue E. van Nieuwenhuyse, Box 1, B-1160 Bruxelles, Belgium
tel: + 32-2-676 7211, fax: + 32-2-676 7300

CEN
Comité Européen de Normalisation
rue de Brederode, Bruxelles, Belgium

CIOMS
c/o WHO
avenue Appia, CH-1211 Geneve 27, Switzerland

CPMP
Secretariat of the Committee for Proprietary Medical Products
DG III BP6 "Pharmaceuticals, veterinary medicines"
Commission of the European Communities
rue de la Loi 200, B-1049 Bruxelles, Belgium
tel: + 32-2-236 03 32/ 235 69 35, fax: + 32-2-236 15 20,
telex: + 21877 COMEU B

Council of Europe
European Pharmacopoeia Commission
226 route de Colmar, BP 907, F-67029 Strasbourg Cedex 1, France
tel: + 33- 88 41 28 83 fax: + 33- 88 41 27 71

EC
European Communities, Office for Official Publications
2, rue Mercier, L-2985 Luxembourg
tel: + 352-499 281, fax: + 352-490 003

EDMUS
European Database for Multiple Sclerosis
Contact: Prof. Christian Confavreux (general information), Mr. Albert Biron (technical information)
Clinique de Neurologie, Hôpital Neurologique,
59 boulevard Pinel, F-69003 Lyon, France
tel: + 33-72 35 72 22, fax: + 33-72 35 73 51

EFPIA
European Federation of Pharmaceutical Industries Associations
250 avenue Louise, Bruxelles, Belgium
tel: + 32-2-640 6815, fax: + 32-2-647 6049

EGA
European Generics Association
76 rue Lesbroussart, B-1050 Bruxelles, Belgium
tel: + 32-2-646 7017, fax: + 32-2-646 7222

European Association of Hospital Pharmacists
Klinikum Stieglitz, Apotheker,
Hindenburgdamm 30, D-12203 Berlin, Germany
tel: + 49-30-79 82 05 0, fax: + 49-30-79 84 14 1

European Organization for Quality
Section for quality in the pharmaceutical industry
Contact: Mr. Lars Färstedt
AB Astra, S-151 85 Södertalje, Sweden
tel: + 46-8 55 32 62 72, fax: + 46-8 55 32 88 32

EORTC
European Organization for Research and Treatment of Cancer
EORTC Data Center and Coordinating Office
Boulevard de Waterloo 125, B-1000 Bruxelles, Belgium
tel: + 32-2-539 28 05

IFAPP
International Federation of Associations of Pharmaceutical Physicians
President: Dr. Luciano M. Fucella, c/o Tecnofarmaci
Via Enrico Nöe 23, I-20133 Milano, Italy
tel: + 39-2-706 346 20, fax: + 39-2-706 352 53

IFPMA
International Federation of Pharmaceutical Manufacturers Associations
(represents the pharma industry in its dealings with WHO and other UN bodies)
30, rue de St. Jean, P.O. Box 9, CH-1211 Geneve 18, Switzerland
tel: + 41-22-340 1200, fax: + 41-22-340 1380

IPEC
International Pharmaceutical Excipients Council
(international harmonization of excipient standards)
Bureaux Europe, 20 place des Halles, F-67000 Strasbourg, France
tel: + 33-88 52 26 26, 75 75 00, fax: + 33-88 52 26 25

NLN
Nordic Council on Medicines
Box 26, S-751 03 Uppsala, Sweden
tel: + 46-18-17 47 00, fax: + 46-18-54 15 80

PIC
Pharmaceutical Inspection Convention
c/o EFTA Secretariat
9-11, rue de Varembé, CH-1202 Geneva, Switzerland

PMA
Pharmaceutical Manufacturers Association
(US pharmaceutical manufacturers association)
Hoge Wei 10, B-1930 Zaventem, Belgium
tel: + 32-3 725 3567, fax: + 32-2 725 3677

RAPS
Regulatory Affairs Professionals Society Europe
83 avenue E. Mounier, Box 4, B-1200 Bruxelles, Belgium
tel: + 32-2-772 92 47, fax: + 32-2-772 72 37

UNICE
Union of Industrial and Employers' Confederations of Europe
40 rue Joseph II, Box 4, B-1040 Bruxelles, Belgium
tel: + 32-2-237 6511, fax: + 32-2-231 1445, telex: 26013

WFPMM
World Federation of Proprietary Medicine Manufacturers
15 Sydney House, Woodstock Road, London W4 1DP,
United Kingdom
tel: + 44-81-747 8709, fax: + 44-81-747 8711

WHO
World Health Organisation
Collaborating Centre for International Drug Monitoring
Box 26, S-75103 Uppsala, Sweden
tel: + 46-18-17 46 00, 17 48 50, fax: + 46-18-54 85 66

WHO
World Health Organisation
Publications, distribution and sales
CH-1211 Geneve 27, Switzerland
tel: + 41-22-791 21 11, fax: + 41-22-791 07 46

WHO
World Health Organisation
Regional Office for Europe
P.O. Box 100, Veitvet, N-0518 Oslo, Norway
tel: + 47-22-16 98 10, fax: + 47-22-16 98 18

G. Pöch

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