

Consultative Document

Interchangeable multi-source pharmaceutical products: WHO draft guideline on marketing authorization requirements

I. Introduction

The competitive pricing that results from the marketing of generic versions of off-patent pharmaceutical products significantly reduces drug costs. Before issuing a marketing authorization for a multi-source (generic) pharmaceutical product the national regulatory authority has to assess if it is therapeutically equivalent and interchangeable with the brand product marketed by the innovator company. Drug regulators attending the Sixth International Conference of Drug Regulatory Authorities (ICDRA) in Ottawa, Canada, in 1991, recommended that WHO should develop global standards and requirements for regulatory assessment and marketing authorization of interchangeable multi-source pharmaceutical products. Proposals for such guidelines are offered in this consultative document.

The term "generic pharmaceutical product" has somewhat different meanings in different jurisdictions, and in this document use of the term is avoided as much as possible, and the term "multi-source pharmaceutical product" has been applied. However, where the term "generic product" had to be used in this document it means a pharma-

ceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company, and marketed after expiry of patent or other exclusivity rights. Generic products may be marketed either under the nonproprietary approved name or under a new brand (proprietary) name. They may sometimes be marketed in dosage forms and/or strengths different from those of the innovator products.

The WHO Guidelines are based on provisions already elaborated by a number of drug regulatory authorities such as Australia, Canada, the European Union countries, Hungary, Japan, the Nordic countries, and the United States. Every care has been taken in developing the WHO Guidelines as a practicable administrative and regulatory tool for the broader constituency of WHO's Member States.

It is the expectation of WHO that all pharmaceutical products, whether purchased on tender or supplied through the public or private sector, are subjected to the same requirements for marketing authorization by the national drug regulatory authority. This is to assure that all available pharmaceutical products are safe, efficacious and of good quality and, when applicable, therapeutically equivalent and interchangeable. Bilateral or multilateral collaboration in regulatory affairs between the drug regulatory authorities assists countries with limited resources. Exchange of evaluation reports on the same product from the same manufacturer can accelerate the adoption of sound decisions at the national level. At the moment, confidentiality requirements

These proposed guidelines remain subject to consultation. Comments, which are invited from all interested parties, should be received by 31 August 1994 in:
The Division of Drug Management & Policies,
World Health Organization, 1211 Geneva 27, Switzerland

can, in some cases, restrict the exchange of assessment reports and the sharing of information on specific pharmaceutical products among drug regulatory authorities. Pharmaceutical companies and their representative bodies should be encouraged to adopt a policy of allowing such exchanges among national drug regulatory authorities providing confidentiality can be assured.

These Guidelines confirm that equivalence between interchangeable multi-source pharmaceutical products is one of the most important items which should be considered in every case as part of the marketing authorization procedure for products which contain established ingredients. In many cases data from bioequivalence studies involving human subjects are necessary to demonstrate equivalence, as part of the assessment of the safety and efficacy of the pharmaceutical product. The implementation of the Guideline, therefore, has both ethical and resource implications which need to be considered in those cases where evidence of equivalence is deemed necessary. Under the Guideline, the equivalence data need to be provided for each of the countries in which a multi-source product is to be marketed, and this could mean that studies on the same product have to be repeated for each country, in order to demonstrate equivalence (and hence interchangeability) with existing products for that particular market. Replication of such studies is not only wasteful of resources, but can also result in unnecessary exposure of volunteers and patients to risk, or potential risk, without specific benefit. Notwithstanding the potential problems which have been identified, it seems necessary to investigate further the feasibility of establishing a system of international reference products for determining equivalence.

A system of international reference products with documented quality, clinical efficacy and safety, including bioavailability should provide information particularly for developing countries as a basis for making decisions about the marketing authorization of multi-source, interchangeable pharmaceutical products. Furthermore, it could help to avoid unnecessary human studies through agreements that products intended for supply to different countries need only be tested once against the international reference product. Finally, an international reference product system could encourage the adoption of uniform bioavailability and quality standards for products in international commerce.

It is hoped, on the basis of further consultation, to seek formal acceptance of the WHO Guidelines by Member States as a contribution to harmonization of standards internationally, and to facilitate regulatory assessment and international movement of safe and efficacious pharmaceutical products of good quality.

II. Definition of terms

Definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

Bioavailability

The rate and extent of absorption of an active drug ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.

Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent and their bio-availabilities (rate and extent of absorption) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Dosage form

The form of the completed pharmaceutical product, e.g., tablet, capsule, elixir, injection, suppository.

Equivalence

Two pharmaceutical products are equivalent if they are pharmaceutically equivalent and after administration in the same molar dose their effects, with respect to both efficacy and safety, will be essentially the same.

Generic product

The term "generic product" has somewhat different meanings in different jurisdictions and in this document use of the term is avoided as much as possible, and the term "multi-source pharmaceutical product" has been applied. However, where the term "generic product" had to be used in this document it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights.

Generic products may be marketed either under the nonproprietary approved name (INN) or under a new brand (proprietary) name. They may some-

times be marketed in dosage forms and/or strengths different from those of the innovator products.

Innovator pharmaceutical product

Generally, the innovator product is that which was first authorized for marketing, as a patented drug, on the basis of documentation of safety, quality and efficacy (according to contemporary requirements).

In the case of drugs which have been available for many years, it may not be possible to identify an innovator pharmaceutical product.

Interchangeable pharmaceutical product

An interchangeable pharmaceutical product is one which is equivalent to a reference product.

Multi-source pharmaceutical products

Multi-source pharmaceutical products are pharmaceutically equivalent drug products that may or may not be equivalent. Multi-source pharmaceutical products that are equivalent are interchangeable.

Pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form that meet the same or comparable standards and are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in product performance (in dissolution rate and/or bioavailability).

Reference listed pharmaceutical product

A pharmaceutical product already marketed, with which the new product is intended to be interchanged in clinical practice. The reference listed product may be the innovator product, or, where multiple interchangeable pharmaceutical products are already marketed, the product which is the market leader may be used.

III. Regulatory assessment of interchangeable multi-source pharmaceutical products

III.1. General considerations

The appropriate governmental authority should ensure that all pharmaceutical products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises

and practices employed to manufacture, store and distribute these products comply with requirements to ensure the continued conformity of the products to these standards until such time as they are delivered to the end user.

These objectives can ideally be accomplished effectively only if a mandatory system of marketing authorization for pharmaceutical products and licensing their manufacturers, importing agents and distributors is in place and adequate resources are available for implementation of these regulations. Health authorities in countries with limited resources have less capacity to undertake these tasks. To assure the quality of imported pharmaceutical products and drug substances, they are dependent on authoritative, reliable, and independent information from the drug regulatory authority of the exporting country. This information, including information on the regulatory status of a pharmaceutical product, and the manufacturer's compliance with GMP (Good Manufacturing Practices) in the exporting country, is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce which provides a channel of communication between regulatory authorities in the importing and exporting countries (Resolutions WHA41.16 and WHA45.26).

The essential functions and responsibilities of a drug regulatory authority are further elaborated by WHO in the Guiding Principles for Small National Drug Regulatory Authorities (*WHO Technical Report Series*, No. 790: 64-79, 1990 and No. 825: 62-74, 1992).

III.2. Multi-source products and interchangeability

There are often economic pressures favouring the use of generic products. In some cases this can result in the purchase on contract of generic products by procurement agencies without prior licensing by the drug regulatory authority. However, all pharmaceutical products, including generic products, should be used in a country only after approval by the appropriate drug regulatory authority. Equally, pharmaceutical products intended exclusively for export should be subject to the same controls and marketing authorization requirements in regard to quality, safety and efficacy as pharmaceutical products intended for the domestic market in the exporting country.

Nominally equivalent interchangeable (generic) pharmaceutical products should contain the same

amount of the same therapeutically active ingredients in the same dosage form and they should meet required pharmacopoeial standards. However, they are usually not identical and in some instances their clinical interchangeability may be in question. Although differences in colour, shape and flavour are obvious and sometimes disconcerting to the patient, they are often inconsequential to the performance of the pharmaceutical product. However differences in sensitizing potential due to the use of different excipients and differences in stability and bioavailability could have obvious clinical implications. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of such pharmaceutical products, but also their interchangeability one with another and with the original innovative pharmaceutical product. This concept of interchangeability applies not only to the dosage form but also to the instructions for use and even to the packaging specifications, when these are critical to stability and shelf-life.

Regulatory authorities should require that documentation of a generic pharmaceutical product addresses three sets of criteria. These relate to:

- manufacturing (GMP) and quality control;
- product characteristics and labelling; and
- equivalence with an interchangeable marketed pharmaceutical product.

Assessment of equivalence will normally require an *in vivo* study, or a justification that such a study should not be required in a particular case. *In vivo* study approaches include bioequivalence studies, pharmacodynamic studies, and comparative clinical trials. In selected cases *in vitro* studies may be sufficient to provide some indication of equivalence (see Section V.2, 4). The regulatory authority should be in a position to help local manufacturers by advising them on drugs that pose potential bioavailability problems and therefore need *in vivo* studies.

III.3. Technical data for regulatory assessment

For pharmaceutical products indicated for standard, well-established uses and that contain established ingredients, the following elements of information usually suffice as the basis both for marketing authorization and for a computerized data retrieval system:

- name of the product;
- active ingredient(s) (by international nonproprietary name(s)); their source; description of manufacturing methods and in-process controls;
- type of dosage form;
- route of administration;
- main therapeutic category;
- complete quantitative formula with justification and method of manufacture of the dosage form;
- quality control specifications for starting materials, intermediates and the final dosage form product; batch results, including, where appropriate, the batch(es) used in bioequivalence studies;
- batch number, manufacturing date;
- indications, dosage, method of use;
- contraindications, warnings, precautions, drug interactions;
- use in pregnancy and other special groups of patients;
- adverse effects;
- overdose;
- equivalence data (comparative bioavailability, pharmacodynamic or clinical studies and comparative *in vitro* dissolution tests);
- stability data, shelf-life, recommended storage conditions;
- container, packaging, labelling;
- intended method of distribution:
 - controlled drug; prescription item;
 - pharmacy sale; general sale;
- manufacturer; licensing status (date of most recent inspection, date of licence and who issued the licence);
- importer/distributor;
- regulatory status in the exporting country and, where available, summary documents of

regulatory assessment from the exporting country; regulatory status in other countries.

If the dosage form is a novel one intended to modify the drug delivery, such as a delayed-release tablet, or if a different route of administration is proposed, supporting data, including clinical studies, will normally be required.

III.4. Product information and promotion

The product information intended for prescribers and end-users should be available for all generic products authorized for marketing. The content of this information should be approved as a part of the product authorization. This information should be updated based on current information. The wording and illustrations used in subsequent promotion of the product should be fully consistent with this approved product information. All promotional activities should respect the WHO Ethical Criteria for Medicinal Drug Promotion (Resolution WHA41.17, May 1988).

III.5. Mutual acceptance of assessment data

Bilateral or multilateral collaboration between the drug regulatory authorities assists countries with limited resources. Sharing responsibilities in assessment and enhancing mutual cooperation provides a wider spectrum of expertise for evaluation. Harmonization of registration requirements between the drug regulatory authorities for registration of generics can accelerate the approval process. Furthermore, an agreed mechanism of quality assurance in relation to the assessment work of collaborating agencies is vital.

Exchange of evaluation reports on the same pharmaceutical product from the same manufacturer can accelerate the adoption of sound decisions at the national level. In some instances when the collaboration between authorities has been well established, even mutual recognition of approvals could take place.

At the moment, confidentiality requirements can restrict the exchange of evaluation reports and the sharing of information between drug regulatory agencies. Pharmaceutical companies and their representative bodies should be encouraged to adopt a policy of allowing such exchanges between national drug regulatory authorities providing confidentiality can be assured.

IV. Equivalence studies needed for marketing authorization

IV.1. Documentation of equivalence for marketing authorization

Pharmaceutically equivalent multi-source pharmaceutical products should be shown to be equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

- (a) Comparative bioavailability (bioequivalence) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.
- (b) Comparative pharmacodynamic studies in humans.
- (c) Comparative clinical trials.
- (d) *In vitro* tests such as *in vitro* dissolution.

Each of these four modalities is discussed in subsequent sections of this guideline and special guidance is provided to conduct an assessment of bioequivalence studies. Other modalities have been used to assess bioequivalence, such as bioequivalence studies in animals, but are not discussed in this guideline because this approach is not accepted worldwide.

The application of any test procedure in the documentation of equivalence between two pharmaceutical products by a registration authority depends on many factors. These factors include characteristics of the active drug substance and the drug product and availability of resources for the conduct of a specific type of study. Where a drug produces meaningful concentrations in an accessible biologic fluid, such as plasma, bioequivalence studies are preferred. Where a drug does not produce measurable concentrations in an accessible biologic fluid, comparative clinical trials or pharmacodynamic studies may be necessary to document equivalence. If resources are limited, *in vitro* testing, preferably based on a documented *in vitro/in vivo* correlation, may sometimes provide some indication of equivalence between two pharmaceutical products.

Additional criteria that indicate when equivalence studies are necessary are discussed in the following two sections of the guideline (IV.2 and IV.3).

IV.2. When equivalence studies are not necessary

For certain formulations and circumstances, equivalence between two pharmaceutical products may be considered self-evident with no further requirement for documentation. Examples include:

- (a) When multi-source pharmaceutical products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations;
- (b) When multi-source pharmaceutical products are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that affects gastrointestinal transit or absorption of the active substance;
- (c) When multi-source pharmaceutical products are a gas;
- (d) When the multi-source pharmaceutical products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;
- (e) When multi-source pharmaceutical products are otic or ophthalmic products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
- (f) When multi-source pharmaceutical products are topical products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
- (g) When multi-source pharmaceutical products are inhalation products or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and contain the same active substance(s) in the same concentration and the same excipients in essentially the same concentrations. Special *in vitro* testing may be required to document comparable device performance of the multi-source inhalation product.

IV.3. When equivalence studies are necessary and types of studies required

Except for the dosage forms listed in Section IV.2, this guideline recommends that documentation of equivalence be requested by registration authorities

for a multi-source pharmaceutical product in which the product is compared to the corresponding approved pharmaceutical product. Studies must be carried out using the formulation intended for marketing (see also Section IX, "Choice of reference products"). For certain drugs and dosage forms, subsequently termed "problem pharmaceutical products", *in vivo* documentation of equivalence, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. Examples of these drugs and dosage forms are listed below.

- (a) Oral immediate release pharmaceutical products with systemic action:
 - (i) indicated for serious conditions requiring assured therapeutic response;
 - (ii) narrow therapeutic window/safety margin; steep dose-response curve;
 - (iii) pharmacokinetics complicated by variable or incomplete absorption (<70%) or absorption window, nonlinear pharmacokinetics, presystemic elimination/high first-pass metabolism >70%;
 - (iv) unfavourable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability, etc.;
 - (v) documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations;
 - (vi) where a high ratio of excipients to active ingredients exists.
- (b) Non-oral and non-parenteral immediate release pharmaceutical products designed to act by systemic absorption.
- (c) Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption.
- (d) Rational fixed combination products (see WHO Technical Report Series No. 825, 1992).
- (e) Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove therapeutic equivalence. This does not, however, exclude the potential need for drug concen-

tration measurements in order to assess unintended partial absorption.

In certain circumstances, equivalence may be assessed by the use of *in vitro* dissolution testing. Examples where dissolution testing may be considered acceptable include:

- (a) Drugs not defined as problem pharmaceutical products;
- (b) Different strengths of a multi-source formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:
 - the qualitative composition between the strengths is essentially the same;
 - the ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
 - an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
 - pharmacokinetics have been shown to be linear over the therapeutic dose range.

Although this Guideline comments primarily on registration requirements for multi-source pharmaceutical products, it is to be noted that *in vitro* dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval (see Section VIII, page 83).

V. Tests for equivalence

V.1. Design and conduct of bioequivalence studies in man

The bioequivalence studies should be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP).

V.1.1. Subjects

(a) Selection of subjects

The subject population for bioequivalence studies should be as homogenous as possible and therefore studies should generally be performed with healthy volunteers in order to reduce variability other than in the pharmaceutical products. Clear criteria for inclusion/exclusion should be stated. If feasible, they should include males and females (however, the risk to women will need to be considered on an individual basis and, if necessary, a warning issued to them about any possible dangers to the fetus if they should become pregnant). They should normally be in the age range of 18 to 55 years with a weight within the normal range according to accepted life tables. The subjects should preferably be non-smokers. If smokers are included they should be identified as such. The suitability of the volunteers should be screened using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual drug being investigated.

(b) Patients versus healthy volunteers

If unacceptable pharmacological effects or risk may ensue because of known adverse effects of the active substance for healthy volunteers, it may be necessary to use patients under treatment rather than healthy volunteers. This alternative should be explained by the sponsor.

(c) Monitoring the health of subjects during the study

During the study, the health of volunteers should be monitored so that onset of side-effects, toxicity, or any intercurrent disease may be recorded, and appropriate measures taken.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study takes place.

(d) Genetic phenotyping

Phenotyping and/or genotyping of subjects may be considered for safety reasons and to explore large inter-subject variations.

V.1.2. Design

(a) General study design

The study should be designed so as to set test conditions which reduce intra-subject and inter-subject variability and avoid biased results.

Standardization (exercise, diet, fluid intake, posture, restriction of the intake of alcohol, caffeine, certain fruit juices, and concomitant drugs in the time period before and during the study) is important to minimize the magnitude of variability other than in the pharmaceutical products.

A cross-over design with randomized allocation of volunteers to each leg is the first choice for bioequivalence studies. In these studies a wash-out period between administration of the drug product and the reference product of more than five times the dominant drug half-life is usual, but special consideration will need to be given to extending this period if active metabolites with longer half-lives are produced.

The administration of the product should be standardized with a defined time of day for ingestion, volume of fluid (150 ml is usual) and usually in the fasting state.

(b) Parameters to be assessed

In bioavailability studies the shape of, and the area under, the plasma concentration curve, or the profile of cumulative renal excretion and excretion rate are mostly used to assess extent and rate of absorption. Sampling points or periods should be chosen such that the time versus concentration profile is adequately defined to allow calculation of relevant parameters. From the primary results the bioavailability parameters desired are calculated, such as AUC_{∞} , AUC_t , C_{max} , t_{max} , Ae_{∞} , Ae_t , dAe/dt , or any other justifiable parameters (cf. Appendix 1). The method of calculating AUC-values should be specified. For additional information $t_{1/2}$ and MRT can be calculated. For steady-state studies AUC_t and % peak trough fluctuation can be calculated. The exclusive use of modelled parameters is not recommended unless the pharmacokinetic model has been validated for the active substance and the products.

(c) Additional considerations for complicated drugs

Drugs which would show unacceptable pharmacological effects in volunteers (e.g., serious adverse events, or where the drug is toxic or particularly

potent or the trial necessitates a high dose) may require crossover studies in patients or sometimes parallel group design studies in patients.

Drugs with long half-lives may require a parallel design or the use of truncated Area Under Curve (AUC_t) data or a multi-dose study. Truncated AUC has been defined as AUC up to 72 hours.

Drugs for which the rate of input into the systemic circulation is important may require the collection of more samples around the time of the t_{max} .

Multi-dose studies may be needed for:

- drugs with non-linear kinetics (including those with saturable plasma protein binding);
- cases where the assay sensitivity is too low to cover a large enough portion of the AUC_{∞} ;
- drug substance combinations, if the ratio of plasma concentrations of the individual drug substances is important;
- controlled-release dosage forms.

(d) Number of subjects

The number of subjects required for a sound bioequivalence study is determined by the error variance associated with the primary parameters to be studied (as estimated from a pilot experiment, from previous studies or from published data), by the significance level desired, and by the deviation from the reference product compatible with bioequivalence and with safety and efficacy. It should be calculated by appropriate methods (see Section V.1.7) and should not be smaller than 12. In most of the cases 18–24 subjects may be needed.* The number of recruited subjects should always be justified.

(e) Chemical analysis

Knowledge of the stability of the active substance and/or its biotransformation product in the sample material is a prerequisite for obtaining reliable results.

* See: Diletti, E., Hauschke, D., Steinijans, V.W. Sample size determination for bioequivalence assessment by means of confidence intervals. *International Journal of Clinical Pharmacology, Therapeutics and Toxicology*, 1991, **29**:1-8; Hauschke, D., Steinijans, V.W., Diletti, E., Burke, M. Sample size determination for bioequivalence assessment using a multiplicative model. *Journal of Pharmacokinetics & Biopharmacy*, 1992, **20**:559-563; and Phillips, K.E. Power of the two one-sided tests procedure in bioequivalence. *Journal of Pharmacokinetics & Biopharmacy*, 1990, **18**:137-144).

V.1.3. Studies of metabolites

Use of metabolite data in bioequivalence studies requires careful consideration. Generally, evaluation of bioequivalence will be based upon the measured concentrations of the pharmacologically active drug substance and its active metabolite(s) if present. If it is impossible to measure the active drug substance, a major biotransformation product may be used. However, both parent and metabolite must exhibit linear pharmacokinetics. The measurement of concentrations of biotransformation product is essential if the substance studied is a prodrug. If urinary excretion (rate) is measured, the product determined should represent a major fraction of the dose (>40%). Although measurement of a major active metabolite is usually acceptable, measurement of an inactive metabolite can only rarely be justified.

V.1.4. Measurement of individual isomers for chiral drug substance products

A non-stereoselective assay is currently acceptable for bioequivalence studies of immediate release formulations.

V.1.5. Validation of analytical test methods

All analytical test methods must be well-characterized, fully validated and documented. They should meet requirements of specificity, accuracy, sensitivity and precision. For this item reference is made to the Conference Report on Analytical Validation: Bioavailability, Bio-equivalence and Pharmacokinetic Studies, *Pharmaceutical Research*, Vol. 9, No. 4, 1992. Results of validation should be reported. Some important points are:

- validation comprises before-study and within-study phases;
- validation must cover the intended use of the assay;
- the calibration range must be appropriate to the study samples;
- if an assay is to be used at different sites, it must be validated at each site and cross-site comparability must be established;
- an assay which is not in regular use requires sufficient revalidation to show that it is performed according to the original validated specifications

(the revalidation study must be documented, usually as an appendix to the study report);

- within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged;
- if different studies are to be compared and the samples from the different studies have been assayed by different methods and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.

Results of validation should be reported.

V.1.6. Sample retention

Sufficient samples of each batch of the pharmaceutical products used in the studies, and a record of their analyses and characteristics, must be kept for reference under appropriate storage conditions as guided by national regulations. When specifically requested these reserve samples may be required by the authorities to recheck the products.

V.1.7. Statistical analysis and acceptance criteria**(a) General aspects**

The primary concern in bioequivalence assessment is to limit the risk of accepting equivalence if it does not hold true. Thus the risk (α) is that which the regulatory agencies are willing to accept for erroneously concluding equivalence.

The statistical method of choice at present is to derive a parametric or non-parametric 100 (1-2 α)% confidence interval, and to decide for equivalence if the confidence interval is fully contained within a clinically relevant and justified acceptance range. Alpha is set at 5% leading, in the parametric case, to the shortest (conventional) 90% confidence interval based on an analysis of variance or, in the non-parametric case, to the 90% confidence intervals.*

The statistical procedures should be specified before the data collection starts (see Appendix 2, page 84). The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e., leading to the same decision whether the new formulation is compared to reference product or reference product to the new formulation).

* See: Hauschke, D. et al. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 1990; **28**:72-78. Hollander M., Wolfe, D.A. *Nonparametric Statistical Methods*. New York: John Wiley & Sons, 1973, Chapter 4.3.

Concentration and concentration-related quantities like AUC, rate constants and half-lives should preferably be analyzed after logarithmic transformation; t_{\max} will usually be analysed without such transformation.

If t_{\max} is to be subjected to a statistical analysis this should be based on non-parametric methods. Other parameters may also be evaluated by non-parametric methods, in which case descriptive statistics should be given that do not require specific distributional assumptions, e.g., medians instead of means.

Assumptions of the design or analysis should be addressed, and the possibility of differing variations in the formulations should be investigated. This covers investigation of period effects, sequence or carry-over effects, and homogeneity of variance (homoscedascity).

Outlying observations should be reviewed for their impact on the conclusions. Medical or pharmacokinetic explanations for such observations should be sought.

(b) Acceptance ranges

Regarding AUC, the 90% confidence interval should generally be within the acceptance range 80 to 125%. For drugs with a particularly narrow therapeutic range, the AUC acceptance range may need to be smaller, and this should be justified clinically.

C_{\max} does not characterize the rate of absorption particularly well and there is no consensus on any other parameter which might be more suitable. The acceptance range for C_{\max} may be wider than for the AUC (see Appendix 2, page 84).

V.1.8. Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with Good Clinical Practice rules (see WHO Guideline for GCP for Trials on Pharmaceutical Products). The responsible investigators should sign for their respective sections of the report. Names and affiliations of the responsible investigators, site of the study and period of its execution should be stated. The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the test product(s) should be given. The analytical validation report should be attached. Results of *in vitro* dissolution tests should be provided. In addition, the applicant should submit a signed

statement confirming the identity of the test product with the pharmaceutical product which is submitted for registration.

All results should be presented in a clear way. The procedure for calculating the parameters used (e.g., AUC) from the raw data should be specified. Deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual plasma concentration/time curves should be drawn on a linear/linear, and facultatively also on a lin/log scale. All individual data and results should be given, also of eventually dropped-out subjects. Drop-out and withdrawal of subjects should be reported and accounted for. Test results of representative samples should be included.

The statistical report should be sufficiently detailed, so as to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

V.2. Pharmacodynamic studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product, e.g., for topical products without an intended absorption of the drug into the systemic circulation.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP (see WHO Guideline for GCP for Trials on Pharmaceutical Products) must be followed.

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by means of measuring pharmacodynamic drug responses.

1. The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.

2. The methodology must be validated for precision, accuracy, reproducibility and specificity.

3. Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects. Investigation of dose-response relationships may be a necessary part of the design.

4. The response should be measured quantitatively under double-blind conditions and be recordable in a machine-produced or machine-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. In those instances where such measurements are not possible, recordings on visual analog scales may be used. In other instances where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.

5. Non-responders should be excluded from the study by prior screening. The criteria by which responders versus non-responders are identified must be stated in the protocol.

6. In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.

7. The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.

8. A cross-over design can be used. Where this is not appropriate a parallel group study design should be chosen.

In studies in which continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations were measured, and parameters can be derived which describe the area under the effect-time curve, the maximum response and the time when maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle, the same as outlined for the bioequivalence studies. However, a correction for the potential non-linearity of

the relationship between the dose and the area under the effect-time curve should be performed on the basis of the outcome of the dose-ranging study as mentioned above. However, it should be noted that the conventional acceptance range as applied for bioequivalence assessment is not appropriate in most of the cases but should be defined on a case-by-case basis and described in the protocol.

V.3. Clinical trials

The methodology issues for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic endpoint have not yet been discussed as extensively as for bioequivalence trials. However, important items can be identified which need to be defined in the protocol:

- (a) the target parameters from which the intensity and the onset, if applicable and relevant, of the response are to be derived;
- (b) the acceptance range must be defined on the basis of clinical knowledge and judgement on a case-by-case basis and described in the protocol (the conventional acceptance range as applied for bioequivalence assessment is not appropriate);
- (c) the statistical procedures must take into consideration that the conventional testing approach is not suitable for confirming equivalence;
- (d) where appropriate, a placebo leg should be included in the design;
- (e) in some cases, it is relevant to include safety endpoints in the final comparative assessments.

V.4. *In vitro* dissolution

Comparative *in vitro* dissolution studies may be useful in the documentation of equivalence between two multi-source pharmaceutical products. The application of *in vitro* dissolution testing as the sole documentation of equivalence is recommended only for drugs that are not problem pharmaceutical products (see Section IV.3, page 76). Because of many limitations associated with the use of *in vitro* dissolution in the documentation of equivalence, this Guideline recommends that its application for this purpose be kept to a minimum. The Guideline recognizes that where *in vivo* equivalence studies cannot be performed, appropriate dissolution data may identify inadequate release of an active drug substance from a formulation.

Approval of multi-source formulations using comparative *in vitro* dissolution studies should be based on generation of comparative dissolution profiles rather than single point dissolution tests, such as are described in various compendia. Development and application of specifications and statistical methods to define nonequivalence are appropriate. These specifications and methods are most reasonable with suitable product development studies that generate formulations with different performance characteristics. In the absence of this formulation development, specifications for *in vitro* dissolution should be drawn from the pilot (bio-batch) or production batch(es) used in the documentation of equivalence.

VI. "In vitro" dissolution tests

The value of an *in vitro* dissolution test to assess equivalence is increased if suitable development and validation studies on the dissolution procedure are performed. These studies may involve the manufacture of different pharmaceutical formulations in the drug development process to identify formulation, or manufacture process variables that affect *in vivo* performance, as assessed, for example, through a bioequivalence study. With the availability of different formulations with variable performance characteristics, the possibility for developing discriminatory *in vitro* dissolution tests exists.

VI.1. Dissolution testing for product development and registration purposes

In product development, dissolution tests should attempt to discriminate differences in formulation and/or process variables. In this respect generation of drug release profiles (3 or 4 time-points) is preferred rather than single points.

For registration/licensing purposes a minimum of two batches of the test product should be sampled and a minimum of 6 dosage units should be taken from each batch. These batches should be on industrial scale (normally not less than 100 000 units). If pilot batches are used, the applicant should provide a justification. Dissolution testing should also be completed on the same batches that had been used for bioequivalence studies.

The following data should be recorded and included in the registration dossiers:

- (a) Comparative results for test and reference products after intervals appropriate for products

and conditions under investigation (normally minimum three sampling times).

- (b) For each sampling time, the observed data, individual values, the range and the coefficient of variation (relative standard deviation) should be reported.

- (c) The analytical method should be described together with information on validation relative to the dosage form under investigation (see WHO recommendations on analytical validation: WHO Technical Report Series No.823, 1992, pp.117-121 and No.790, 1990, pp.10-13).

- (d) Information on batches tested:

- for test products: batch no., date of manufacture, scale, (pilot plant, full production);
- for reference products: batch no., expiry date, date of manufacture when available.

VI.2. Dissolution test as a quality control method

The dissolution test selected in the analytical development phase should as a minimum, allow the impact of the formulation and process variables on the release rate to be determined. In other words, the test ought to have a discriminating power regarding differences in formulation and process parameters. Attempts should also be made to correlate the dissolution characteristics with *in vivo* performance (in those cases where bioavailability studies are deemed to be necessary).

The test may be considered as a useful check for several characteristics of the dosage form:

- particle size distribution, crystal form and other solid state properties of the active ingredients;
- mechanical properties of the form itself (resistance to crushing force for tablets, integrity of the shell for capsules and coated tablets, etc.).

The test is used by the manufacturer on marketed products for verification of the batch-to-batch consistency. It is also used to test release characteristics of a dosage form in storage, i.e., to measure stability of the release rate.

The dissolution test in the individual monograph of *The International Pharmacopoeia* may be useful even for dosage forms including immediate release forms containing freely soluble active ingredients, as a safeguard against occasional grossly

inadequate formulation. Many substances may be considered as potential candidates for the introduction of a dissolution test in *The International Pharmacopoeia*.

VII. Suprabioavailability

A new formulation with increased bioavailability compared to an existing pharmaceutical product is defined as being "suprabioavailable". Options in this situation are:

(i) The dosage form, if reformulated to be bioequivalent with the existing pharmaceutical product could be accepted as interchangeable with the existing pharmaceutical product. This may not be ideal as dosage forms with low bioavailability tend to be variable in performance.

(ii) A dosage form with the content of active substance reduced to allow for the increased bioavailability could be accepted as a new (improved) dosage form. This would normally need to be supported by clinical trial data. Such a pharmaceutical product must not be accepted as interchangeable with the existing pharmaceutical product, and would normally become the reference product for future interchangeable pharmaceutical products. The name of the new pharmaceutical product should preclude confusion with the older approved pharmaceutical product(s).

VIII. Studies need to support new post-marketing manufacturing conditions

With all pharmaceutical products, extensive *in vitro* and/or *in vivo* testing may be required, if significant post-marketing changes are made. Significant changes include changes in: (i) formulation; (ii) site

of manufacture; (iii) process of manufacture; and (iv) manufacturing equipment. The types and extent of further testing required depend on the magnitude of the changes made. If a major change is made, the product might become a new pharmaceutical product. Reference should be made to national regulatory authorities in this regard.

IX. Choice of reference product

The innovator pharmaceutical product is usually the most logical reference product for related generics because, in general, its quality will have been well assessed and its efficacy and safety will have been securely established in clinical trials and post-marketing monitoring schemes. There is, however, currently no global agreement on the selection of a reference product. The selection is made variably at national level by the drug regulatory authority having regard either to the most widely used "leading" product within the market or the pharmaceutical product that was first to be approved within that market. The possibility exists for significant differences to emerge between reference products adopted in different countries.

This being so, consideration needs to be given to the feasibility of developing reference materials on a global basis. The pharmaceutical industry and its representative bodies should be invited to collaborate in the preparation, maintenance and international acceptance of a system of international reference standards for pharmaceutical products with defined quality and bioavailability characteristics.

Appendix 1: Explanation of the symbols in paragraph V.1.2 and other commonly used pharmacokinetic abbreviations

C_{max}	The observed maximum or peak concentration of drug (or metabolite) in plasma, serum or whole blood.	Ae	Cumulative urinary recovery of parent drug (or metabolite). The Ae symbol may be qualified by a specific time (e.g., from zero to 12 hours, Ae_{12}).
C_{min}	Minimum plasma concentration.	Ae_t	Ae from zero to last quantifiable concentration.
C_{max} -ratio	The ratio of geometric means of the test and reference C_{max} values.	Ae_{∞}	Ae from zero to infinite time, obtained by extrapolation.
C_{av}	Average plasma concentration.	Ae_t	Ae over one dosing interval at steady-state.
AUC	The area under the drug (or metabolite) concentration in plasma (or serum or whole blood) versus time curve. The AUC symbol may be qualified by a specific time (e.g., from zero to 12 hours, AUC_{12}).	dAe/dt	Urinary excretion rate of parent drug (or metabolite).
AUC_t	AUC from zero to the last quantifiable concentration.	t_{max}	The time after administration of the drug at which C_{max} is observed.
AUC_{∞}	AUC from zero to infinity, obtained by extrapolation.	t_{max} -diff	The difference of arithmetic means of the test and reference t_{max} values.
AUC_t	AUC over one dosing interval (t) at steady-state.	$t_{1/2}$	Plasma (serum, whole blood) half-life.
AUC-ratio	The ratio of geometric means of the test and reference AUC values.	MRT	Mean residence time.

Appendix 2: Technical aspects of bioequivalence statistics

Introduction: The pharmacokinetic characteristics to be tested, the procedure for testing and the norms to be maintained should be stated beforehand in the protocol. A *post hoc* change of the methods described for the statistical evaluation is only acceptable if protocol adherence would preclude a meaningful evaluation and if such change of procedure has been fully justified.

In testing for equivalence of the main characteristics AUC and C_{max} , the multiplicative model is used which has as consequence that data should be logarithmically transformed before statistical analysis.

Acceptance ranges for main characteristics

- AUC-ratio** The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80 to 1.25. In case of an especially narrow therapeutic range the acceptance range may need to be tightened. A larger acceptance range may be acceptable if clinically appropriate.
- C_{max} -ratio** This measure of relative bioavailability is inherently more variable than e.g., the AUC-ratio, and a wider acceptance range may be appropriate. The range used should be justified taking into account safety and efficacy considerations.
- t_{max} -diff** Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs for a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.