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MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS: GUIDELINES ON REGISTRATION REQUIREMENTS TO ESTABLISH INTERCHANGEABILITY

DRAFT REVISION

This document is a revision of a text drafted by Dr Rein Pähkla, Estonia. The first draft was extensively discussed among the members of the FIP/WHO BCS Task Force by mail, as well as during an informal meeting held in Geneva on 16-18 August 2004. Thereafter further modifications were discussed in a second informal consultation held in New Orleans. Dr Vinod Shah and Dr K. Midha served as rapporteurs of these meetings. The draft was then presented to the 39th WHO Expert Committee on Specifications for Pharmaceutical Preparations. All comments received were collated and categorized by Professor Dressman, Germany, and subsequently discussed during a consultation held on 18-22 July 2005 in Geneva.

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TIMETABLE FOR MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS: GUIDELINES ON REGISTRATION REQUIREMENTS TO ESTABLISH INTERCHANGEABILITY. DRAFT FOR REVISION

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1. INTRODUCTION

This general guidance is intended to provide recommendations to sponsors for the requirements of a multisource (generic) pharmaceutical product approval in their respective countries. The guidance is prepared to provide appropriate *in vivo* and *in vitro* requirements to assure interchangeability of the multisource product without compromising safety, efficacy and pharmaceutical product quality.

The national health and drug regulatory authorities should ensure that all pharmaceutical products subject to their control are in conformity with acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with Good Manufacturing Practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until such time as they are delivered to the end user.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the local authority. Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet (i) GMP, (ii) quality control specifications, and (iii) pharmaceutical product interchangeability. Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety required of the originator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. With some

classes of product, including - most evidently - parenteral formulations of highly water soluble compounds, interchangeability is adequately assured by implementation of GMP and evidence of conformity with relevant pharmacopoeial specifications. For other classes of product, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma, and products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are not addressed in this document, and these products are consequently excluded from consideration.

In order to ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Direct practical demonstration of therapeutic equivalence in a clinical study usually requires large numbers of patients. Such studies in humans can be financially daunting, are many times unnecessary and in certain cases may be unethical. For these reasons the science of bioequivalence testing has been developed over the last forty years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent /alternative and bioequivalent.

Types of *in vivo* bioequivalence studies include pharmacokinetic studies, pharmacodynamic studies and comparative clinical trials. To exert an optimal therapeutic action, an active pharmaceutical ingredient should be delivered to its site(s) of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect, the performance of the pharmaceutical preparation should be well characterized by *in vivo* and/or *in vitro* studies. Direct or indirect comparison of therapeutic performances of two pharmaceutical products containing the same active pharmaceutical ingredient is a prerequisite for interchangeablility between comparator and multisource products. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. In selected cases, *in vitro* dissolution profile comparison of the multisource product with the comparator product or dissolution studies may be sufficient to provide indication of equivalence.

This guideline refers to the marketing of pharmaceutical products that are equivalent and hence intended to be therapeutically equivalent and thus interchangeable but produced by different manufacturers. It should be noted that the concept of interchangeability includes the equivalence of the dosage form as well as the indications and instructions for use. This guidance is generally applicable to orally administered multisource pharmaceutical products, as well as to non-orally administered pharmaceutical products where reliance on systemic exposure measures is suitable to document bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. The WHO guideline should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights (1).

2. DEFINITIONS

Some important terms used in this guideline are defined below. They may have different meanings in other contexts.

Bioavailability
The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. In the majority of cases reliable measurements of drug

concentrations at the site(s) of action are not possible. The substance in general circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can be therefore defined as the rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the general circulation. It is assumed by PK-PD theory that in the same subject an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the site(s) of action.

Bioequivalence
Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavialbility in terms of peak (Cmax and Tmax) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation.

Biopharmaceutics Classification System (BCS)
BCS is a scientific framework for classifying active pharmaceutical ingredients based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product, the BCS takes into account three major factors that govern the rate and extent of drug absorption (exposure) from immediate release oral solid dosage forms: dissolution, solubility, and intestinal permeability.

Biowaiver
The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than *in vivo* bioequivalence test.

Comparator product
Comparator product is a pharmaceutical product with which the new multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality has been established. The selection of the comparator product is usually made at the national level by the drug regulatory authority. A national drug regulatory authority has in principle options which are described in section 6.5.2.

Dosage form
The finished formulation of a pharmaceutical product, e.g. tablet, capsule, suspension, solution for injection, suppository.

Equivalence requirements
In vivo and/or *in vitro* testing requirements for multisource pharmaceutical product approval and marketing authorization.

Equivalence test
Equivalence test is a test that determines the equivalence between the multisource product and the comparator product using *in vivo* and/or *in vitro* approaches.

Fixed-dose combination (FDC)
A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses.
This term is used generically to mean a particular combination of active pharmaceutical

ingredients irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

Fixed-dose combination finished pharmaceutical product (FDC-FPP)
A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

Generic product
A "generic product" is a multisource pharmaceutical product which is intended to be interchangeable with the comparator product. It is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights.

> [***Note from the WHO Secretariat:***
> WHO's Legal Department has commented that the use of the word "usually" in the definition of generic product is not favoured. Please comment.]

Innovator pharmaceutical product
Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy.

Interchangeable pharmaceutical product
An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged in clinical practice.

***In vitro* equivalence test**
In vitro equivalence test is a dissolution test that includes dissolution profiles comparison between the multisource product and the comparator product in three media: pH1.2 HCl, pH 4.5 and pH 6.8.

***In vitro* quality control dissolution test**
Dissolution test procedure identified in the pharmacopoeia, generally a one time point dissolution test for immediate release products and three or more time points dissolution test for modified release products.

Multisource pharmaceutical products
Multisource pharmaceutical products are **intended** to be pharmaceutically equivalent or pharmaceutical alternatives that are bioequivalent and hence are therapeutically equivalent and interchangeable.

Pharmaceutical alternatives
Products are parmaceutical alternative (s) if they contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent with the comparator product.

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

Therapeutic equivalence
Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, will be essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bioequivalence studies such as pharmacokinetic, pharmacodynamic, clinical or *in vitro* studies.

3. DOCUMENTATION OF EQUIVALENCE FOR MARKETING AUTHORIZATION

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product in order to be considered interchangeable. Suitable test methods to assess equivalence are:

(a) comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that are reflective of the systemic exposure;
(b) comparative pharmacodynamic studies in humans;
(c) comparative clinical trials; and
(d) comparative *in vitro* tests.

Applicability of each of these four modalities is discussed in subsequent sections of this guideline. Detailed information is provided to conduct an assessment of equivalence studies using pharmacokinetic measurements and *in vitro* methods, which are currently the most often used methods to document equivalence for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active pharmaceutical ingredient and the pharmaceutical product. Where an active pharmaceutical ingredient produces meaningful concentrations in an accessible biological fluid such as plasma, comparative pharmacokinetic studies can be performed. Where appropriate *in vitro* testing and BCS based biowaivers for immediate release pharmaceutical products can assure equivalence between the multisource product and the comparator product (see sections 5 and 9), *in vitro* studies may be sufficient. Where an active pharmaceutical ingredient does not produce measurable concentrations in an accessible biological fluid, comparative pharmacodynamic studies are a further alternative to document equivalence. Comparative clinical trials may also be used to document equivalence. In certain cases when it is not possible to determine the pharmacokinetic profile or to find suitable pharmacodynamic endpoints, comparative clinical trials can be considered appropriate.

Criteria that indicate when equivalence studies are necessary are discussed in the following two sections of the guideline.

4. WHEN EQUIVALENCE STUDIES ARE NOT NECESSARY

The following types of multisource pharmaceutical products are considered to be equivalent without the need for further documentation:

(a) When the pharmaceutical product is to be administered as an aqueous intravenous solution containing the same active pharmaceutical ingredient in the same molar concentration as the comparator product. Bioequivalence testing is also not required when pharmaceutically equivalent products are to be administered by other parenteral routes (e.g. intramuscular, subcutaneous) as aqueous solutions and contain the same active pharmaceutical ingredient(s) in the same molar concentration and the same or similar excipients in comparable concentrations as in the comparator product. Certain excipients (e.g. buffer, preservative, antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product;

(b) When pharmaceutically equivalent products are solutions for oral use (including syrups, elixirs, tinctures or other soluble forms but not suspensions), contain the active pharmaceutical ingredient in the same molar concentration as comparator product, and contain essentially the same excipients in comparable concentrations. Excipient(s) known to affect gastrointestinal (GI) transit, GI permeability and hence absorption or stability of the active pharmaceutical ingredient in the GI tract should be critically reviewed;

(c) When pharmaceutically equivalent products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;

(d) When pharmaceutically equivalent products are gases;

(e) When pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations. Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided use of these excipients is not expected to affect safety and/or efficacy of the product;

(f) When pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations;

(g) When pharmaceutically equivalent products are aqueous solutions for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device, and contain the same active pharmaceutical ingredient(s) in the same concentration and essentially the same excipients in comparable concentrations. The pharmaceutical product may include different excipients provided their use is not expected to affect safety and/or efficacy of the product.

For elements (b), (c), (e), (f) and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the comparator product. In the event that this information about the comparator product cannot be provided by the applicant and the drug regulatory authority does not have access to these data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

5. WHEN *IN VIVO* EQUIVALENCE STUDIES ARE NECESSARY AND TYPES OF STUDIES REQUIRED

Except for the cases illustrated in Section 4 this guideline recommends that documentation of equivalence with the comparator product be requested by registration authorities for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing (see also Section 6.5).

5.1 *In vivo* studies

For certain medicines and dosage forms, *in vivo* documentation of equivalence, through either a pharmacokinetic bioequivalence study, a comparative pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. *In vivo* documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence (3). Examples are listed below.

(a) Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:

- critical use medicines;
- narrow therapeutic range (efficacy/safety margins); steep dose-response curve;
- documented evidence for bioavailability problems or bio-inequivalence related to the active pharmaceutical ingredient or APIs of similar chemical structure or formulations (unrelated to dissolution problems);
- there is scientific evidence to suggest that either the polymorphs of API, the excipients or the pharmaceutical processes used in manufacturing could affect the bioequivalence.

(b) Non-oral and non-parenteral pharmaceutical products designed to act by systemic absorption (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives, etc.).

(c) Modified release pharmaceutical products designed to act by systemic absorption.[1]

(d) Fixed combination products with systemic action, where at least one of the active pharmaceutical ingredients requires an *in vivo* study. (*Ref* WHO, FDC guide, TRS 929, Annex 5).

(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 equivalence is established through, e.g. comparative clinical or pharmacodynamic, dermatopharmacokinetic studies and/or *in vitro* studies. In certain cases, active pharmaceutical ingredient concentration measurement can be still required for safety reasons in order to assess unintended systemic absorption.

[1] In some instances, the product marketing authorization may be based on *in vitro in vivo* correlation (IVIVC) information and *in vitro* data of modified release drug products, provided it is not the first (original) approval of the modified release dosage form.

5.2 *In vitro* studies

For certain medicines and dosage forms, *in vitro* documentation of equivalence may be appropriate. These studies are addressed in section 9.

6. BIOEQUIVALENCE STUDIES IN HUMANS

6.1 General considerations

6.1.1 Provisions for studies in humans

Pharmacokinetic studies, pharmacodynamic studies and clinical studies are all clinical trials and 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 (4).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki, including respect for persons, beneficence (maximize benefits and minimize harms and wrongs) and non-maleficence (do no harm). as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects.

6.1.2 Justification of human bioequivalence studies

Most pharmacokinetic and pharmacodynamic bioequivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject.

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks/benefits of a particular human study be thoroughly considered and that the chosen solutions be scientifically sound and ethically justified. It is assumed that people involved in the planning of a study are familiar with pharmacokinetic theories underlying bioavailability and bioequivalence studies. In the case of multisource products adequate data concerning the pharmacokinetics or pharmacodynamics of the active pharmaceutical ingredient should be available. Overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the active pharmaceutical ingredient. Information about manufacturing procedures and data from tests performed on the actual product should establish that the investigational product is of suitable quality.

6.1.3 Selection of investigators

Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigator(s) and the sponsor should establish an agreement on the protocol, the monitoring, the auditing, standard operating procedures (SOP) and the allocation of trial-related responsibilities. Identity and duties of the individuals who are responsible for the study and safety of the subjects participating in the study must be specified. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

6.1.4 Study protocol

The bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor, and appended as amendments. The protocol and attachments/appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol and attachments/appendices should be scientifically and ethically appraised by one or, if required, by local laws and regulations, more review bodies (institutional review board, peer review committee, ethics committee, drug regulatory authority, etc.), constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

A signed and dated clinical trial protocol should be presented together with the clinical trial report for the authorities in order to obtain the marketing authorization for the multisource product.

6.2 Study design

Bioequivalence studies are designed to compare the *in vivo* performance of a multisource product with that of a comparator product. Pharmacokinetic bioequivalence studies on products designed to deliver the active pharmaceutical ingredient for systemic exposure serve two purposes: (i) they serve as surrogate for clinical proof of equivalence; and (ii) they provide an *in vivo* measure of pharmaceutical quality. The design of the study should minimize the variability that is not caused by formulation effects and eliminate bias as much as possible. Test conditions should reduce within- and between-subject variability. In general for a pharmacokinetic bioequivalence study involving a multisource and a comparator product, a two-period, single-dose, cross-over study in healthy volunteers will suffice. However, in certain circumstances, an alternate, well-established and statistically appropriate study design should be adopted.

A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for pharmacokinetic bioequivalence studies. Each subject is given the multisource and the comparator product in randomized order. Administrations of each product should be separated by an adequate washout period. The interval (wash-out period) between dosing of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The wash-out period should be the same for all subjects and normally should be more than five times the terminal half-life of the active pharmaceutical ingredient. Special consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under other circumstances. If the product has high variability in elimination rate between subjects, the wash-out period can be longer to account for the elimination rate in subjects with lower elimination rates. Just prior to treatment administration at the second study period, blood samples are collected and assayed for concentration of the API or metabolites. The minimum wash-out period should be at least 7 days. Adequacy of wash-out period can be estimated from the pre-dose concentration of the API and should be less than 5% of Cmax.

It is not foreseen that blood samples be collected for more than 72 hours.

6.2.1 Alternative study designs in patients

For active pharmaceutical ingredients that are very potent or too toxic to administer in the usual dose to healthy volunteers it is recommended that the study be conducted at a lower strength. If the pharmacokinetics are not proportional or if the active pharmaceutical ingredient has solubility issues, it will not be appropriate to extrapolate the bioequivalence results of the lower strength to higher strengths. For these APIs and for those that show unacceptable pharmacological effects in volunteers (e.g. serious adverse events, or where the active pharmaceutical ingredient is toxic or particularly potent, or the trial necessitates a high dose) may require multiple-dose, steady-state, cross-over studies in patients or a parallel group design study in patients. The alternative study design should be justified by the sponsor. In this situation, the sponsor should attempt to enter patients whose disease process is stable for the duration of the pharmacokinetic bioequivalence study.

6.2.2 Considerations for drugs with long elimination half-lives

A single dose cross-over pharmacokinetic bioequivalence study of an oral product of a long elimination half-life drug can be conducted provided an adequate wash-out period is used. If the cross-over study is problematic, a pharmacokinetic bioequivalence study with a parallel design can be used. For either a cross-over or a parallel design study, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the pharmaceutical product and absorption of the active pharmaceutical ingredient. Blood sampling up to 72 hours should be carried out, unless shorter periods can be justified. The number of subjects should be derived from statistical calculations but generally more subjects are needed for parallel study design compared with cross-over study design.

6.2.3 Considerations for multiple dose studies

In certain situations multiple dose studies may be considered appropriate. Multiple dose studies in patients are most useful in cases where the medicine is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses (see also 6.2.1). In this case, a multiple dose cross-over study in patients may be performed without interrupting therapy. Evaluation of such studies can be based either on pharmacokinetic or pharmacodynamic endpoints, although it is likely that pharmacodynamic endpoints would require much larger number of patients than pharmacokinetic end points.

In multiple dose studies the dosage regimen should follow the usual dosage recommendations.

Other situations in which multiple dose studies may be appropriate are as follows:

- drugs that exhibit non-linear kinetics at steady state (e.g. saturable metabolism, active secretion);
- cases where the assay sensitivity is too low to adequately characterize pharmacokinetic profile after single dose;
- extended-release dosage forms with tendency to accumulation (in addition to single-dose study);

In steady-state studies the wash-out of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the

terminal half-life). Appropriate dosage administration and sampling should be carried out to document the attainment of steady state.

6.2.4 Considerations for modified release products

Modified release products include extended release products and delayed release products. Extended release products are also known as controlled release, prolonged release and sustained release products.

Bioavailability data must be obtained for all modified-release products. A single dose, non-replicate cross-over, fasting study comparing the highest strength of the multisource and the comparator product should be performed. Single dose studies are preferred to multiple dose studies as single dose studies are considered more sensitive to measure the release of active pharmaceutical ingredient from the pharmaceutical product into the systemic circulation. Multiple dose studies may need to be considered for extended-release dosage forms with tendency to accumulation (in addition to single-dose study).

The comparator product in this study should be a pharmaceutically equivalent modified release product, which is already marketed. The pharmacokinetic bioequivalence criteria for modified release products are basically the same as for conventional release dosage forms.

Co-administration of food with oral pharmaceutical products may influence drug bioavailability and in certain cases also pharmacokinetic bioequivalence. In addition to physiological changes in the gastro-intestinal tract, food can affect the release of the active pharmaceutical ingredient from the formulation. A concern with modified release products is the possibility that food may trigger a sudden and abrupt release of the active pharmaceutical ingredient leading to “dose dumping”. This would most likely be manifested as a spike in plasma concentration time profile. Therefore, a pharmacokinetic bioequivalence study under fed conditions is generally required for orally administered modified release pharmaceutical products. Absence of either fed or fasting study should be justified by the applicant. A fed pharmacokinetic bioequivalence trial should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 min.) before taking the medicine (see also Section 6.4.). The most appropriate meal would be one of high lipid content in accordance with local diet and customs. The caloric breakdown and composition of the test meal should be provided in the study report.

6.3 Subjects

6.3.1 Number of subjects

The number of subjects required for a sound pharmacokinetic bioequivalence study is determined by:

- the error variance (coefficient of variation) 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 (5%);
- by the power level desired;
- by the expected mean deviation from the reference product compatible with bioequivalence and with safety and efficacy;
- with 90% Confidence Interval around the geometric mean ratio to be within 80%-125% bioequivalence limits for log transformed data.

The number of subjects to be used in the study should be estimated by considering the standards that must be passed. It should be calculated by appropriate methods (see statistical analysis and acceptance criteria below). The number of recruited subjects should always be justified with the sample size calculation provided in the study protocol. A minimum of 12 subjects is required.

6.3.2 Drop-outs and withdrawals

Sponsors should enter a sufficient number of subjects in the study to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse drug reaction, personal reasons) must be reported.

Sponsors who wish to replace drop-outs during the study or consider an add-on design should indicate this intention in the protocol.

It is more appropriate to recruit into the study more subjects than the sample size calculation requires. These subjects are designated as extras. The protocol should state whether samples from extra subjects will be assayed if not required for statistical analysis.

If the bioequivalence study was performed with the appropriate size but bioequivalence cannot be demonstrated because of a result of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study. Combining is acceptable only in the case when the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and SOPs, and must be given appropriate statistical treatment, including consideration of consumer risk.

6.3.3 Selection of subjects

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion/exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both genders, the sponsor may wish to include both, males and females in the study. The risk to women will need to be considered on an individual basis, and if necessary, they should be warned of any possible dangers to the foetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before the first and last doses of the study.

Generally subjects should be between the ages of 18-55 years, and of weight within the normal range according to accepted life tables. The subjects should be without known history of alcohol or drug abuse problems and should preferably be non-smokers.

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 active pharmaceutical ingredient being investigated, e.g. an electrocardiogram if the active pharmaceutical ingredient has a cardiac effect. Ability to understand and comply with the study protocol has to be assessed. Subjects who are being or have been previously treated for any gastrointestinal problems, or convulsive, depressive, or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

In case the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria have to be adjusted accordingly.

6.3.4 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. The incidence, severity, and duration of adverse reactions and side effects observed during the study must be reported. The probability that an adverse effect is drug-induced is to be judged by the investigator.

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 is conducted.

6.3.5 Considerations for genetic phenotyping

Phenotyping for metabolizing activity can be of importance for studies with high clearance drugs that are metabolized by enzymes that are subject to genetic polymorphism, e.g. propranolol. Slow metabolizers will in these cases have a higher bioavailability of the parent drug, while the bioavailability of possible active metabolites will be lower. Phenotyping of subjects can be considered for studies with drugs that show phenotype-linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed in the two groups of subjects.

Phenotyping could also be important for safety reasons, determination of sampling times and wash-out periods in cross-over design studies.

6.4 Study standardization

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

Volunteers should not take any other medicine, including alcoholic beverages and over-the-counter (OTC) medicines, for an appropriate interval before – as well as during – the study. In the event of emergency, the use of any medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as much as possible to limit effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each study day. The time of day for study drug administration should be specified.

Medicines are usually given after overnight fasting for at least 10 hours. However, alcohol-free and xanthine-free clear fluids are permissible during the night prior to the study. On the morning of the study no water is allowed for one hour before drug administration. The dose should be taken with water of a standard volume (usually 150-250 ml). Two hours after drug administration water is permitted ad *libitum*. A standard meal is usually provided 4 hours after drug administration. All meals should be standardized and of similar composition and quantity during each study period.

Some medicines are normally given with food to reduce gastrointestinal side effects; in certain cases co-administration with food increases bioavailability of orally administered preparations. If the

labelling states that the pharmaceutical product should be taken with food then a fed study should be used to assess bioequivalence.

Fed studies are also required in bioequivalence studies of modified release formulations. The objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. The test meal should be selected based on local custom and diet and should be completed within 20 min. Drugs should be administered according to the dosing regimen, within 30 min. after the meal has been completed.

6. 5 Investigational product

6.5.1 Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability) but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch control results of the test product, the lot numbers of both test and comparator products and the expiration date for the comparator product should be stated.

Samples ideally should be taken from batches of industrial scale. When this is not feasible pilot or small-scale production batches may be used provided that they are not smaller than 10% of expected full production batches, or 100 000 units whichever is higher (unless otherwise justified), and are produced with the similar equipment, machinery and process as that planned for commercial production batches. If the product is subjected to further scale-up, this should be properly validated.

It is recommended that potency and *in vitro* dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to performance of an equivalence study. Content of the active pharmaceutical ingredient(s) of the comparator product should be close to the label claim, and the difference between two products should preferably not be more than +/-5%.

6.5.2 Choice of comparator product

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in premarketing studies and post-marketing monitoring schemes.
For some pharmaceutical products an innovator product cannot be identified; in some cases an innovator product is not available on the market. A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and to a lack of interchangeability with the innovator.

The selection of the comparator product is usually made at the national level by the drug regulatory authority. A national drug regulatory authority has in principle options which are listed in order of preference:

- to choose the innovator product, if this product has been granted a national marketing authorization, for which quality, safety and efficacy has been established *("national innovator")*; or

- to choose the WHO comparator product, all of which have been granted marketing authorization, for which quality, safety and efficacy have been established, and which have reference to a manufacturing site ("*WHO comparator product"*) and which is to be purchased in that country as cited in the list; or

- to choose the innovator product, i.e. a product for which a marketing authorization has been granted in a well regulated (ICH or associated country) and which is to be purchased from that market *("ICH et al innovator")*; or

- in the case an innovator product cannot be identified – or is no longer available - and no appropriate product is mentioned in the above referred WHO list, the choice of the comparator must be made carefully and must be justified comprehensively by the applicant. The most important selection criteria in order of preference are: - approval in ICH- and associated countries, - "pre-qualified" by WHO, - extensive documented use in clinical trials reported in peer-reviewed scientific journals, and - long and unproblematic post-market surveillance. *("well selected comparator"*)

A product approved based on comparison with a non domestic comparator product may not be interchangeable with currently marketed domestic products.

In the context of regional harmonization efforts, there may be advantages to choose a list regional comparator products for which quality, safety and efficacy has been established, in order to increase access to medicines

WHO has initiated a list of comparator products ("WHO *comparator product"*) for equivalence assessment of interchangeable multisource products which provides recommendations for choosing comparator product in cases where the innovator product is not available (2).

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with lot number and expiry date.

6.6 Study conduct

6.6.1 Selection of dose

In bioequivalence studies the molar equivalent dose of multisource and comparator product should be used.

Generally the marketed strength with the greatest sensitivity to bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose may be employed when analytical difficulties exist. In this case the total single dose should not exceed the maximal daily dose of the dosage regimen.

In certain cases a study performed with a lower strength can be considered acceptable if a lower strength is chosen for reasons of safety. Alternatively the application of AUC truncated to 3 x median t_{max} of the comparator formulation would avoid problems of lack of assay sensitivity in many cases.

6.6.2 Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should include a pre-dose sample, at least 1-2 points before C_{max}, 2 points around C_{max} and 3-4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. For most medicines the number of necessary samples can be higher because of between-subject differences in absorption and elimination rate to enable accurate determination of the maximum concentration of the active pharmaceutical ingredient in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the AUC (0 -> infinity) can be accrued, but it is not necessary to sample more than 72 hours. An alternative approach is to use the truncated AUC approach, which curtails the numbers of samples required to define the elimination phase and allows more samples to be devoted to the elucidation of C_{max} (see Section 6.11.4). The exact timing for sample collection depends on the nature of the active pharmaceutical ingredient and the input function from the administered dosage form.

Treatments should be separated by adequate wash-out periods. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Preferably the interval should not be less than 5 terminal elimination half-lives of the active compound or metabolite, if the latter is measured. Normally the interval between study days should not exceed 3-4 weeks. If a longer wash-out period is required a parallel design can be considered.

6.6.3 Sample collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the active pharmaceutical ingredient. In most cases the API or metabolites are measured in serum or plasma. If the active pharmaceutical ingredient is excreted predominantly unchanged in the urine, urine can be sampled. When urine is collected at the study centre the volume of each sample must be measured immediately after collection and included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the t_{max} and the maximum concentration.

Blood samples should be processed and stored under conditions that have shown not to cause degradation of the analytes. This can be proven by analysing duplicate quality control (QC) samples during the analytical period. Quality control samples must be prepared in the fluid of interest (e.g. plasma), including concentrations at least at the low, middle and high segments of the calibration range. The quality control samples must be stored with the study samples and analysed with each set of study samples for each analytical run.

Sample collection methodology should be specified in the study protocol.

6.6.4 Parameters to be assessed

In bioavailability studies the shape of and the area under the plasma concentration versus time curves are mostly used to assess extent (AUC) and rate (Cmax, tmax)of absorption. Sampling points or periods should be chosen such that the concentration versus time profile is adequately defined to allow calculation of relevant parameters. For single dose studies the following parameters should be measured or calculated:

- Area under the plasma/serum/blood concentration-time curve from time zero to time t (AUC_{0-t}), where t is the last time point with measurable concentration for individual formulation. The method of calculating AUC-values should be specified. In general AUC should be calculated using the linear/log trapezoidal integration method. The exclusive use of compartmental based parameters is not recommended.

- C_{max} is the maximum or peak concentration observed representing peak exposure of active pharmaceutical ingredient (or metabolite) in plasma, serum or whole blood.

AUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition it is recommended that the following parameters be estimated:

- Area under the plasma/serum/blood concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\beta$; C_{last} is the last measurable drug concentration and β is the terminal or elimination rate constant calculated according to an appropriate method.

- t_{max} – the time after administration of the drug at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

- $T_{1/2}$ – the plasma (serum, whole blood) half-life.

For steady-state studies the following parameters can be calculated:

- $AUC\tau$ - AUC over one dosing interval (τ) at steady-state.
- C_{max}.
- C_{min} – concentration at the end of a dosing interval.
- peak trough fluctuation – % difference between C_{max} and C_{min}.

When urine samples are used cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_{max}.

6.6.5 Studies of metabolites

Generally evaluation of pharmacokinetic bioequivalence will be based upon the measured concentrations of the parent drug released from the dosage form rather than the metabolite. Concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution and elimination. It is important to state *a priori* in the study protocol which chemical entities (pro-drug, drug (active pharmaceutical ingredient), metabolite) will be analyzed in the samples.

In some situations measurements of metabolite concentrations may be necessary instead of parent drug:

- The measurement of concentrations of therapeutically active metabolite is acceptable if the substance studied is a pro-drug.

- If an active metabolite is formed as a result of gut wall or other presystemic metabolic process(es) and the metabolite contributes meaningfully to safety and/or efficacy, it is recommended that both the metabolite and the parent drug concentrations be measured.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time or when the parent compound is unstable in the biological matrix.

It is important to note that measurement of one analyte, active pharmaceutical ingredient or metabolite, allows the risk of making a Type-I error (the consumer risk) to remain at the 5% level. However, if more than one of several analytes is selected retrospectively as the bioequivalence determinant, then the consumer and producer risks change (5).

When measuring the active metabolites wash-out period and sampling times may need to be adjusted in order to adequately characterize the pharmacokinetic profile of the metabolite.

6.6.6 Measurement of individual enantiomers

A non-stereoselective assay is currently acceptable for most pharmacokinetic bioequivalence studies. When the enantiomers have very different pharmacological or metabolic profiles, assays that distinguish between the enantiomers of a chiral active pharmaceutical ingredient may be appropriate. Stereoselective assay is also preferred in the case when systemic availability of different enantiomers is demonstrated to be non-linear.

6.6.7 Use of fed state studies in bioequivalence determination

6.6.7.1 Immediate release formulations

Fasted state studies are generally preferred. When the product is known to cause gastrointestinal disturbances if given in the fasted state, or if labelling restricts to administration to the fed state only, then the fed state pharmacokinetic bioequivalence study becomes the preferred method. The details of the meal may depend on local diet and customs.

6.6.7.2 Modified release formulations

Food effect studies are necessary for all multisource modified release formulations to ensure the absence of "dose dumping". The latter signals a formulation failure such that the dose is released all at once rather than over an extended period of time. This results in a "spike" in plasma concentrations time profile. A high fat meal is recommended to provide maximum perturbation to challenge the robustness of release from the formulation with respect to prandial state. The composition of the meal may depend on local diet and customs. (See also Section 6.2.4)

In addition to the fast state studies, see also section 9.3.3 dose proportional studies.

6.7 Active pharmaceutical ingredients' quantification

All analytical test methods used to determine the active compound and/or its biotransformation product in the biological fluid must be well-characterized, fully validated and documented. The objective of the validation is to demonstrate that a particular method used for quantitative

measurement of analytes in a given biological matrix, such as blood, plasma, serum or urine, is reliable and reproducible for the intended use.

Applicable principles of GLP should be followed in the conduct of chemical analysis (6). Bioanalytical methods should meet the requirements of specificity, sensitivity, accuracy, precision and reproducibility. Knowledge of the stability of the active pharmaceutical ingredient and/or its biotransformation product in the sample material is a prerequisite for obtaining reliable results.

The Bioanalytical Method Validation Conference held in 2000 made several recommendations for the conduct of analysis of biological samples in a pharmacokinetic study (7). Some important recommendations are:

- Validation comprises before-study and within-study phases. During the pre-study phase stability of the stock solution and spiked samples in the biological matrix, specificity, sensitivity, accuracy, precision and reproducibility should be provided. Within-study validation proves the stability of samples collected during clinical trial under storage conditions and confirms the accuracy and precision of the determinations.

- Validation must cover the intended use of the assay.

- The calibration range must be appropriate to the study samples. A calibration curve should be prepared in the same biological matrix as the samples in the intended study by spiking the matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample, and six to eight non-zero samples covering the expected range. Concentrations of standards should be chosen on the basis of the concentration range expected in a particular study.

- If an assay is to be used at different sites, it must be validated at each site, and cross-site comparability established.

- An assay which is not in regular use requires sufficient revalidation to show that its performance is according to the original validated test procedures. 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.

- Spiked quality control samples at a minimum of three different concentrations in duplicate should be used for accepting or rejecting the analytical run.

- All the samples for one subject (all periods) should be analysed in the same analytical run, if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol, and/or SOP. All experiments used to make claims or draw conclusions about the validity of the method should be presented in a report (method validation report). Any modification of the

method during the analysis of study samples will require adequate revalidation. Results of study sample determination should be reported in the analytical report together with calibration and QC sample results, repeat analyses (if any), and a representative number of sample chromatograms.

6.8 Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that the clinically significant difference in bioavailability is unlikely. The statistical procedures should be specified before the data collection starts in the protocol.

The statistical method for testing pharmacokinetic bioequivalence is based upon the determination of the 90% confidence interval around the ratio of the log transformed population means (multisource/ comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance (8). To establish pharmacokinetic bioequivalence the calculated confidence interval should fall within a preset bioequivalence limit. 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 multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and C_{max}) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of common or natural logs should be consistent and should be stated in the study report. Logarithmically transformed concentration-dependent pharmacokinetic parameters should be analysed using ANOVA. Usually the ANOVA model includes the formulation, period, sequence or carry-over and subject factors.

Parametric (normal-theory) methods are recommended for the analysis of log-transformed bioequivalence measures. The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is contained in the stated limits. Due to the nature of normal-theory confidence intervals this is equivalent to carrying out two one-sided tests of hypothesis at the 5% level of significance (8,9). The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products.

The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery, if required.

Usually for t_{max} descriptive statistics should be given. If t_{max} is to be subjected to a statistical analysis this should be based on non-parametric methods and should be applied to untransformed data. If t_{max} is analysed a sufficient number of samples around predicted maximal concentrations should have been taken to ensure the correctness of t_{max} estimate. For parameters describing the elimination phase ($T_{1/2,}$) normally only descriptive statistics should be given.

Methods for identifying and handling of possible outlier data should be specified in the protocol. Medical or pharmacokinetic explanations for such observations should be sought and discussed. As outliers may be indicative of product failure, *post hoc* deletion of outlier values is generally discouraged. An approach of dealing with data containing outliers is to apply distribution-free (non-parametric), statistical methods (10).

If the distribution of log transformed data is not normal, non-parametric statistical methods can be considered. The justification of the intent to use non-parametric statistical methods should be included a priori in the protocol.

6.9 Acceptance ranges

AUC-ratio
The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80-1.25. If the therapeutic range is particularly narrow the acceptance range may need to be reduced based on clinical justification. A larger acceptance range may be acceptable in exceptional cases if justified clinically.

C_{max}-ratio
In general acceptance limit 0.80-1.25 should be applied to the C_{max}-ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and in certain cases a wider acceptance range (e.g. 0.75-1.33) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations. In exceptional cases, a simple requirement for the point estimate to fall within a bioequivalence limits of 0.80-1.25 may be acceptable with appropriate justification in terms of safety and efficacy.

t_{max}-difference
Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

For other pharmacokinetic parameters the same considerations as outlined above apply.

6.10 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 (4). The respective ICH guideline (11) can be used in the preparation of the study report. The responsible investigator(s) should sign for their respective sections of the report. Names and affiliations of the responsible investigator(s), 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 tests product(s) should be given. 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.

The bioanalytical validation report (see Section 6.7) should be attached. The bioanalytical report should include the data of calibrations and quality control samples. A representative number of chromatograms or other raw data should be included covering the whole calibration range, quality control samples and specimens from the clinical trial.

All results should be presented clearly. All measured concentrations for each subject and the sampling time should be tabulated for each formulation. Also tabulated results showing of API concentration analyses according to analytical run (including runs excluded from further calculations, including all calibration standards and quality control samples of the respective run) should be presented. In this tabulation, date of run, subject, study period, applied product

(multisource or comparator) and time elapsed from drug application to blood sampling should be provided in an easily identifiable form. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual blood concentration/time curves should be drawn on a linear/linear, and linear/log scale. All individual data and results should be given, including those subjects who dropped out. The drop-out and/or withdrawn subjects should be reported and accounted for.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject-formulation combination together with descriptive statistics. 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.

6.11 Special considerations

6.11.1 Fixed combination products

If the pharmacokinetic bioequivalence of combination products is assessed by *in vivo* studies the study design should follow the same general principles as described in previous sections. In this study the multisource combination product should be compared with the pharmaceutically equivalent comparator combination product. In certain cases (e.g. when no comparator combination product is : available on the market) separate products administered in free combination can be used as a comparator (12). Sampling times should be chosen in such a way that pharmacokinetic parameters of all active ingredients could be adequately assessed. The bioanalytical method should be validated with respect to all compounds measured. Statistical analyses should be performed with pharmacokinetic data of all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

6.11.2 Clinically important variations in bioavailability

Innovators should make all efforts to provide formulations with good bioavailability characteristics. A "high variable" pharmaceutical product is one in which the active pharmaceutical ingredient itself is not highly variable, but the formulation is one of poor pharmaceutical quality. If a better formulation is being developed over time by the innovator this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range compared to an existing pharmaceutical product is not interchangeable by definition. Adjusting the strength to compensate with regard to sub- or supra-bioavailability in comparison with the comparator product falls outside the scope of this document, as the pre-requisite of pharmaceutical equivalence is not fullfilled.

6.11.3 "Highly variable drugs"

A "highly variable drug" has been defined as active pharmaceutical ingredient with a within-subject variability of $\geq$ 30% in terms of the ANOVA-CV (13). Moreover "highly variable drugs" are generally safe drugs with shallow dose-response curves. Proving the bioequivalence of dug products containing "highly variable drugs" is problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. Thus large numbers of subjects must be enrolled in studies involving

highly variable drugs to achieve adequate statistical power. The following approaches to this problem are currently being applied in different drug regulatory jurisdictions:

(i) some regulatory authority permit the use of broadened bioequivalence limits provided there is adequate justification (14), for example, the regulatory agency could broaden the bioequivalence limits from 0.8-1.25 to 0.75-1.33 taking into consideration the therapeutic category of the drug;

(ii) some regulatory authority permit the use of scaling to broaden the bioequivalence limits. In a two-period design, the limits are scaled to the residual standard deviation, or in a replicate design, to the within-subject standard deviation of the comparator formulation (15-17);

(iii) some regulatory authority allow the following acceptance criteria: "Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic AUC and Cmax between test and reference products is within the acceptable range of log(0.8) - log(1.25) (18); however, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied:

(a) the total sample size of the initial bioequivalence study is not less than 20 (n=10/group) or pooled sample size of the initial and add-on subject studies is not less than 30;

(b) the ratio of geometric LS means of AUC and Cmax between the multisource and comparator product are between 0.9-1.11; and

(c) dissolution rates of test and reference products are evaluated to be equivalent under all dissolution testing conditions under Sec.3 A.V.

(iv) some do not allow for any adjustments (19).

However, the third rule cannot be applied to slowly dissolving products from which more than 80% of a drug does not dissolve within the final testing time (2 hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests described in Sec.3 A.V." The relevant national/regional regulatory authority of the country should adopt any one of these approaches prospectively to regulate the market authorization of highly variable pharmaceutical products.

6.11.4 Application of truncated AUC in bioequivalence determination

In bioavailability studies it is generally recommended that plasma concentrations should be followed for at least three half-lives post-dose. Potent drugs found in plasma at low concentrations usually require sophisticated and expensive equipment to be able to measure the active pharmaceutical ingredient in the terminal portions of the plasma concentration versus time curve. In consideration of the bioequivalence of immediate release formulations for systemic delivery, the most important portion of the plasma concentration versus time curve is until the absorption phase is complete. On the other hand the disposition phase does not illustrate formulation differences between the multisource product and comparator product in bioequivalence decision-making process (20 and 21) . Gaureault examined the use of partial (truncated) AUC using Monte Carlo simulations and found a high degree of concordance between the bioequivalence decision based on the partial area truncated to 4 times tmax and the area extrapolated to infinity. The evidence suggests that for immediate release formulations it is unnecessary to take blood samples beyond 4 times tmax. (22). There are two

important advantages to the use of truncated areas: (i) more blood samples can be clustered around tmax to give greater precision in the estimation of both tmax and Cmax; and (ii) the lack of need for high assay sensitivity in order to define the disposition phase. The applicability of the truncated AUC approach merits particular consideration in the following cases: (i) where low concentrations occur in the terminal portion of the plasma concentration versus time curve, which may not be quantifiable by means of an adequately validated, sensitive analytical method; and (ii) for products of active pharmaceutical ingredients with long half-lives.

7. PHARMACODYNAMIC STUDIES

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products. Pharmacodynamic studies are not recommended for orally administered pharmaceutical products for systemic action when the active pharmaceutical ingredient is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This recommendation arises because variability in pharmacodynamic measures is always greater than that in pharmacokinetic measures. In addition pharmacodynamic measures are often subject to significant placebo effects which add to the variability and complicates experimental design. The result is that often huge numbers of patients would have to be enrolled in pharmacodynamic studies to achieve adequate statistical power. Pharmacodynamic bioequivalence studies may become necessary if quantitative analysis of the active pharmaceutical ingredient and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity (see section on truncated areas, section 6.11.4). Furthermore, pharmacodynamic bioequivalence studies in humans are required if measurements of active pharmaceutical ingredient concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product. In certain treatment categories, such as pharmaceutical products designed to act locally, there is no realistic alternative than to perform pharmacodynamic bioequivalent studies. Pharmacodynamic bioequivalence studies may be appropriate for pharmaceutical products such as topicals and inhalation dosage forms.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP must be followed (4).

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:

- The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the test nor the comparator 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.
- The response should be measured quantitatively preferably under double-blind conditions and be recordable in an instrument-produced or instrument-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 analogue scales may be used. In other instances where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.

- 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.
- 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.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of baseline conditions.
- A cross-over design can be used. Where this is not appropriate a parallel group study design should be chosen.

Selection basis for the multisource and comparator products should be the same as described in section 6.5 .

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 pharmacokinetic 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. However, it should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate in most of the cases but should be justified on a case by case basis and defined in the protocol.

8. CLINICAL TRIALS

In some instances (see example (e) under "*In vivo* studies" above) plasma concentration time-profile data are not suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic bioequivalence studies can be an appropriate tool for establishing equivalence, in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and a comparative clinical trial has to be performed in order to demonstrate equivalence between two formulations. In the cases when equivalence can be assessed by a pharmacokinetic bioequivalence study, the pharmacokinetic bioequivalence study is preferred because comparative clinical trial is less sensitive. Huge numbers of subjects are required to achieve statistical power. For example, 8600 patients were calculated to give adequate power to detect a 20% improvement in response to the study drug compared with placebo (23). Similarly it was calculated that 2600 myocardial infarct patients were required to show a 16% risk reduction. Comparison of two formulations of the same active pharmaceutical ingredient based on such endpoints would require even greater numbers of subjects (24)

If a clinical bioequivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the pharmacokinetic bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in pharmacokinetic bioequivalence studies.

The following items are important and need to be defined in the protocol in advance.

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 pharmacokinetic bioequivalence trials. However, important items can be identified which need to be defined in the protocol:

- The target parameters which usually represent relevant clinical endpoints from which the intensity and the onset, if applicable and relevant, of the response are to be derived.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to pharmacokinetic bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials cannot be based on a general consensus for all the therapeutic classes and indications.
- The presently used statistical method is the confidence interval approach. The main concern is to rule out that the test product is inferior to the comparator pharmaceutical product by more than the specified amount. Hence a one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
- Where appropriate a placebo leg should be included in the design.
  In some cases it is relevant to include safety endpoints in the final comparative assessments.
- Selection basis for the multisource and comparator products should be the same as described in section 6.5 .

9. *IN VITRO* TESTING

Over the past three decades dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a quality control test, is now emerging into a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) a comparative *in vitro* dissolution profile similarity can be used to document equivalence of a multisource with a comparator product (see Section 6.5 for selection of comparator products).

It should be noted that the dissolution tests recommended in *The International Pharmacopoeia* (25) for quality control have been designed to be compatible with the biowaiver dissolution tests, they may not yet fulfil all requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for quality control purposes in other pharmacopoeia in general do not correspond to the test conditions required for evaluating bioequivalence of multisource products and should not be applied for this purpose.

9.1 *In vitro* testing and the Biopharmaceutics Classification System (BCS)

9.1.1 Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) is based on aqueous solubility and intestinal permeability of the drug substance. It classifies the active pharmaceutical ingredient (API) into one of four classes:

Class 1- High Solubility, High Permeability
Class 2 - Low Solubility, High Permeability
Class 3 - High Solubility, Low Permeability
Class 4 - Low Solubility, Low Permeability

Combining the dissolution of the drug product with these two properties of the API, the three major factors that govern the rate and extent of drug absorption from immediate release solid dosage forms are taken into account (26). With respect to dissolution properties, immediate release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of scientific principles of solubility and permeability and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate release drug products (27). Oral drug products *not* eligible for a so-called "biowaiver" based on the BCS approach are described under Section 5.1.a.

9.1.1.1 High solubility

An API is considered highly soluble when the highest dose recommended by WHO (if the API appears on the WHO Model List of Essential Medicines) or highest dose strength available on the market as a oral solid dosage form (if the API does not appear on the WHO Model List of Essential Medicines) is soluble in 250 mL or less of aqueous media over the pH range of 1.2 to 6.8. The pH-solubility profile of the API should be determined at 37 ± 1°C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended. Initial recommendations in the BCS Guidance (27) suggested that the solubility should be measured over a pH range of 1.2 to 7.5. But successive scientific discussions and publications suggest that a pH range of 1.2 to 6.8 is more appropriate (28).

9.1.1.2 High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison to an intravenous comparator dose. Initial recommendation in the BCS Guidance (27) suggested an absorption value of $\geq$ 90% as a prerequisite for classification as highly permeable. However, successive scientific discussions and scientific publications suggested relaxing the criteria to 85% absorption for classifying a drug as highly permeable (28). Acceptable alternative test methods for permeability determination of the drug substance include:

(i) *in vivo* intestinal perfusion in humans, or
(ii) *in vitro* permeation using excised human or animal intestinal tissue.

When one of these two alternative methods is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to the permeability of a reference compound whose fraction dose absorbed has been documented to be at least 85%.

Supportive data can be provided by the following additional test methods:

(iii) *in vivo* or *in situ* intestinal perfusion using animal models, or

(iv) *in vitro* permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) using a method validated using APIs with known permeabilities,

although data from either of the two latter methods would not be considered acceptable on a stand-alone basis. In these experiments high permeability is assessed with respect to a high permeability of a series of reference compounds with documented permeabilities and fraction absorbed values, including some for which fraction dose absorbed is at least 85% (28).

9.1.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the BCS

For exemption from an *in vivo* pharmacokinetic bioequivalence study, an immediate release multisource product should exhibit very rapid or rapid *in vitro* dissolution characteristics (see below), depending on the BCS properties of the API. *In vitro* data should also demonstrate the similarity of dissolution profiles between the test and comparator products.

9.1.2.1 Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% (total dissolution) of the labelled amount of the drug substance dissolves in 15 minutes or less using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media: (i) pH 1.2 HCl solution; (ii) a pH 4.5 acetate buffer; and (iii) a pH 6.8 phosphate buffer.

9.1.2.2 Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% (total dissolution) of the labelled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media: (i) pH 1.2 HCl solution; (ii) a pH 4.5 acetate buffer; and (iii) a pH 6.8 phosphate buffer.

9.2 Qualification for a biowaiver based on the BCS

A biowaiver based on the Biopharmaceutics Classification Scheme (BCS) considers:

a) the solubility and permeability of the active pharmaceutical ingredient (see section 9.1),
b) the dissolution profile similarity of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media (see below),
c) the excipients used in the formulation (see below), and
d) the risks of an incorrect biowaiver decision in terms of the therapeutic index and indications for the active pharmaceutical ingredient (see section 5.1 for cases where an *in vivo* study would be required to demonstrate bioequivalence).

Only when there is an acceptable benefit/risk balance in terms of public health and risk to the individual patient should bioequivalence testing according to the guidelines given in this Section be permitted.

Risk analysis

The risk of reaching an inappropriate decision that the multisource product is equivalent to the comparator product can be reduced by correct classification of the API and by following the recommendations for dissolution testing and comparison of the dissolution profiles. In all cases it should be further demonstrated that the excipients included in the formulation of the multisource product are well established for products containing that API, and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g. via effects on gastrointestinal motility or interactions with transport processes), or which might lead to interactions that alter the pharmacokinetics of the API. The underlying basic principle being that the products are consistently of the same quality, i.e. produced in accordance with good manufacturing practices (GMP).

Excipients

Evidence, that each excipient present in the multisource product is well established and does not effect gastrointestinal motility or other process affecting absorption, can be documented using part of the following informaton:

i) the excipient is present in the comparator product, or the excipient is present in a number of other products which contain the same API as the multisource drug product and which have marketing authorizations in countries participating in the International Committee on Harmonisation (ICH) or associated countries, and
ii) the excipient is present in the multisource product in an amount similar to that in the comparator, or the excipient is present in the multisource drug product in an amount typically used for that type of dosage form.

Information with respect to composition of drug products with marketing authorization is available on several websites of some national drug regulatory authorities. Examples of excipients known to have caused bioinequivalence that would not have been predicted by dissolution testing include surfactants, mannitol and sorbitol.

As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate equivalence decision using a biowaiver based on the BCS.

Sub- and supra-bioavailable products

A further consideration is the potential risk to public health and the individual patient, should an inappropriate decision with respect to bioequivalence be reached. Essentially there are two possible negative outcomes.

The first arises when the multisource product is sub-bioavailable. In this case substitution of the comparator with the multisource product could lead to reduced therapeutic efficacy. APIs which must reach a certain concentration to be effective (e.g. antibiotics) are most susceptible to problems with sub-bioavailability.

The second negative outcome arises when the multisource product is supra-bioavailable. In this case substitution of the comparator with the multisource product could lead to toxicity. APIs which exhibit toxic effects at concentrations close to the therapeutic range are most susceptible to problems with

supra-bioavailability. For these reasons, both the indication and therapeutic index are important considerations in determining whether the biowaiver based on BCS can be applied or not.

Dissolution Profile Comparison

Approval of multisource formulations using comparative *in vitro* dissolution studies should be based on generation of comparative dissolution profiles rather than a single point dissolution test. When comparing the multisource and comparator products, dissolution profiles can be compared using a similarity factor (f_2). This is a model independent mathematical approach for comparing the dissolution profiles of two products. The dissolution profile of the two products (multisource (test) and comparator (reference) or two strengths from a given manufacturer should be made under the same test conditions. The dissolution profile of the multisource and comparator products should be made under the same test conditions using an apparatus that conforms to the Ph. Int. specifications using either the paddle method at 75 rpm or the basket method at 100 rpm in pH 1.2, 4.5 and 6.8 buffers (Int.Ph. buffers are recommended; alternative compendial buffers with same pH and buffer capacity are also acceptable) at 37°C.

Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product completely *for example* at 10, 15, 20, 30, 45 and 60 minutes. A minimum of 12 dosage units of each product (multisource and comparator) should be evaluated (29,30).

When comparing the multisource and comparator products, dissolution profiles can be compared using a similarity factor (f_2). Data with less than 20% variance at the first time-point and less than 10% variance at subsequent time-points can be used for the f_2 calculation, noting that a maximum of one time point should be considered after 85% dissolution of the comparator product has been reached. An f_2 value of 50 or greater (50-100) reflects sameness or equivalence of the two curves and thus equivalence of the *in vitro* performance of the two products. The similarity factor f_2 is to be computed using the equation:

$$f_2 = 50 \log \{[1+(1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} 100\}$$

where R_t and T_t are the cumulative percentage of the drug dissolved at each of the selected n time points of the comparator (reference) and multisource (test) product respectively (4, 5).

If the comparator and multisource products are very rapidly dissolving, i.e. more than 85% dissolution in 15 minutes or less in all three media using the recommended test method, a profile comparison is not necessary.

Other appropriate statistical methods can also be used for dissolution profile comparison, provided that the same criterion is used for acceptance (maximum 10% difference between the profiles).

9.2.1 Dissolution criteria for biowaivers based on the BCS according to API properties

The major application of BCS is to provide criteria for biowaiver of multisource products. Kasim et al. (31), Lindenberg et al. (32) have partially classified the drugs listed under WHO Model List of Essential Medicines according to available literature data for solubility and permeability and a series of individual biowaiver monographs has been initiated in J. Pharm Sci. (33). To date the BCS Guidance of the HHS-FDA recommends the biowaiver only for drug products containing Class 1

drugs (27). These biowaiver criteria have been described as very conservative. Discussions at scientific workshops after the guidance became available and in subsequent publications recommended that biowaiver can, in principle, be extended to:

(i) BCS class 3 drug products, if the multisource and comparator product are very rapidly dissolving (85% or greater in 15 minutes or less at pH 1.2, 4.5 and 6.8), and

(ii) BCS class 2 weak acids if the multisource product is rapidly dissolving (85% or greater in pH 6.8 in 30 minutes or less) and its dissolution profile is similar to that of the comparator product at pH 1.2, 4.5 and 6.8 under the dissolution test conditions described in section 9.2.

On the basis of the above concept WHO has collated a draft proposal to waive *in vivo* bioequivalence requirements for the WHO Model List of Essential Medicines immediate release, solid oral dosage forms (34).

In summary, biowaivers for solid oral dosage forms based on BCS can be considered under following conditions:

1. Dosage forms of APIs which are highly soluble, highly permeable (BCS Class 1), and are rapidly dissolving are eligible for a biowaiver based on the BCS provided:

   (i) The dosage form is *rapidly dissolving* (as defined in section 9.1.2.2.) and the dissolution profile of the multisource product is similar to that of the comparator product at pH 1.2, pH 4.5 and pH 6.8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm (as described in section 9.2**.**) and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion).

   (ii) If both the comparator and the multisource dosage forms are *very rapidly dissolving* (as defined in section 9.1.2.1.) the two products are deemed equivalent and a profile comparison is not necessary.

2. Dosage forms of APIs which are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers provided all the criteria described in section 9.2**.** are met and the risk/benefit is additionally addressed in terms of extent, site and mechanism of absorption.

   In general, the risks of reaching an inappropriate biowaiver decision need to be more critically evaluated when the extent of absorption is lower (especially if $f_{abs} < 50\%$), if the sites of absorption are restricted to the proximal regions in the gastrointestinal tract and if the mechanism of absorption is subject to induction/competition. If any of these cases apply, the excipients used will also need to be scrutinized carefully in terms of both qualitative and quantitative composition – the greater the deviation from the comparator composition, the greater the risk of an inappropriate biowaiver decision.

   If it is deemed that the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS when both the comparator and the multisource dosage forms are *very rapidly dissolving* (85% dissolution in 15 minutes as described in section 9.1.2.1)

3. Dosage forms of APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability (by definition, BCS Class 2 compounds with weak acidic properties) are eligible for a biowaiver based on BCS provided that criteria b), c) and d) described in section 9.2. are met, that the API has high permeability (corresponding to 85% or greater fraction absorbed) and a dose:solubility ratio of 250 ml or less at pH 6.8, and that the multisource product:

   (i) is *rapidly dissolving* (85% in 30 minutes or less) in pH 6.8 buffer using the general test procedure conforming to section 9.2**.** and

   (ii) The multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product in buffers at the three pH values (pH 1.2, 4.5 and 6.8).

   For multisource products containing Class 2 APIs with dose:solubility ratios of 250 ml or less at pH 6.8, the excipients should additionally be critically evaluated in terms of type and amounts of surfactants in the formulation.

9.3 Biowaivers based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

9.3.1 Proportionally similar formulations

For the purpose of this guidance proportionally similar formulations can be defined in two ways, based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportion between different strengths (e.g. tablet of 50 mg strength has all the inactive ingredients exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).

(ii) For a high potency API (up to 10 mg per dosage unit), where the amount of the API in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ± 10% of the total weight), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering essentially only the amount of the API(s).

9.3.2 Qualification for biowaiver based on dose-proportionality of formulations

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the multisource product at one strength has been shown to be bioequivalent to the corresponding strength of the comparator product. The second requirement is that the further strengths of the multisource product are proportionally similar in formulation to that of the studied strength. When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to the one of the studied strength on a percentage released vs. time basis, the biowaiver procedure can be considered for the further strengths.

As in the case of biowaivers based on BCS, a biowaiver based on dose-proportionality of formulations should only be considered when there is an acceptable benefit/risk balance in terms of public health and risk to the individual patient, as discussed in section 9.2.

9.3.3 Dissolution profile comparison for biowaivers based on dose-proportionality of formulations

As for the biowaiver based on BCS, a model independent mathematical approach (e.g. f_2 test) can be used for comparing the dissolution profiles of two products. The dissolution profile of the two products (multisource (test) and comparator (reference)) should be made under the same test conditions.

The dissolution sampling times for both multisource and comparator product profiles should be the same:

for example for immediate release products 10, 15, 20, 30, 45, 60 minutes
for example for 12 hour extended release products 1, 2, 4, 6 and 8 hours and
for example for 24 hour extended release products 1, 2, 4, 6 , 8 and 16 hours.

Only one time point should be considered after 85% dissolution from the comparator product. An f_2 value of 50 or greater (50-100) reflects equivalence (less than 10% difference) of the two curves, and thus equivalence of *in vitro* performance of the two products. To allow the use of the mean data, the coefficient of variation should not be more than 20% at the earliest time point (e.g. 10 minutes in the case of the example given for immediate release products), and should not be more than 10% at other time points.

9.3.3.1 Immediate release tablets

Different strengths of a multisource formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:

(i) all strengths are proportionally similar in formulation (see definition above);

(ii) 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

(iii) the dissolution profiles between the strengths are similar, $f_2 \geq 50$.

As for the biowaiver based on BCS, if both the multisource and comparator product release 85% or more of the label amount of the API in 15 minutes using all three dissolution media as recommended in 9.2**.**, the profile comparison with an f_2 test is unnecessary.

9.3.3.2 Extended release beaded capsules

For extended release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing active moiety, dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaivers based on dose-proportionality of formulation.

9.3.3.3 Extended release tablets

For extended release tablets, when the multisource product is in the same dosage form but in a different strength, and is proportionally similar in its active and inactive ingredients and has the same drug release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in three diverse pH buffers (between pH 1.2 and 7.5) by the recommended test method.

9.4 Biowaivers for scale-up and post-approval changes

Although this guideline comments primarily on registration requirements for multisource pharmaceutical products, it is to be noted that under certain conditions *in vitro* dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics with minor formulation or manufacturing changes after drug approval.

10. REFERENCES

1. Annex 1 C, Article 39. In: *Marrakesh Agreement Establishing the World Trade Organization.* Marrakesh, GATT, 1994.

2. *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. Thirty-sixth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.* WHO Technical Report Series, No. 902, 2002: 161-180. (update in process)

3. HHS/FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations, March 2003. http://www.fda.gov/cder/guidance/index.htm

4. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *The use of essential drugs. Sixth report of the WHO Expert Committee.* WHO Technical Report Series, No. 850, 1995:97-137.

5. Midha KK, Rawson MJ, Hubbard JW. Commentary: The Role of Metabolites in Bioequivalence. *Pharmaceutical Research,* 2004, 21:1331-1344.

6. OECD Series on Principles of Good Laboratory Practice and compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM (98)17.26.Jan, 1998.

7. Shah VP, Midha KK, Findlay JWA, et al. Bioanalytical Method Validation – A revisit with a decade of progress. *Pharmaceutical Research:* 2000, 17: 1551 – 1557.

8. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal* of *pharmacokinetics and biopharmaceutics*, 1987,15:657-680.

9. Westlake WJ. Bioavailability and Bioequivalence of Pharmaceutical Formulations, in Biopharmaceutical Statistics for Drug Development (Peace KE, ed.), Marcel Dekker, Inc., 1988, 329-352.

10. Hauschke D, Steinijans VW, Diletti E. A distribution-free procedure for the statistical analysis of bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol,* 1990, 28:72-78.

11. ICH E3, Structure and Content of Clinical Study Reports.

12. Guidelines for Registration of fixed dose combination medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical prepatoins. Thirty-nonth report of the WHO Expert Committee.* WHO Technical Report Series, No. 929, *2005, Annex 5*: 94-142.

13. Blume HH, Midha KK. Bio-International 92, Conference on bioavailability, bioequivalence and pharmacokinetic studies. *Journal of Pharmaceutical Sciences*, 1993, 82:1186-1189.

14. Note for Guidance on the investigation of bioavailability and bioequivalence, London, July 2001. Committee for Proprietary Medicinal Products (CPMP). The European Agency for the Evaluation of Medicinal Products - Evaluation of Medicines in Human Use. (http://eudora.org/emea.html)

15. Tothfalusi L, Endrenyi L, Midha KK, Rawson MJ, Hubbard JW. Evaluation of bioequivalence of highly variable drugs. *Pharmaceutical Research,* 2001, 18:728-733.

16. Tothfalusi L, Endrenyi L, Midha KK. Scaling of wider bioequivalence limits for highly variable drugs and for the special case of Cmax. *International Journal of Clinical Pharmacology and Therapeutics,* 2003, 41:217-225.

17. Tothfalusi L, Endrenyi L,. Limits for scaled average bioequivalence of highly variable drugs and drug products. *Pharmaceutical Research,* 2003, 20:382-389.);

18. Guideline for bioequivalence studies of generic products (Japan). http://www.nihs.go.jp/drug/be-guide(e)/Generic/be97E.html

19. Expert Advisory Committee on Bioavailability and Bioequivalence, Record of Proceedings (June 26 and 27, 2003) Health Canada

20. Midha KK, Hubbard JW, Rawson MJ, Gavalas, L., The application of partial areas in the assessment of rate and extent of absorption in bioequivalence studies of conventional release products: experimental evidence. *European Journal of Pharmaceutical Sciences*, 1994, 2:351-363;

21. Midha KK, Hubbard JW, Rawson MJ. Retrospective evaluation of relative extent of absorption by the use of partial areas under the plasma concentration versus time curves in bioequivalence studies of conventional release products. *European Journal of Pharmaceutical Sciences*, 1996, 4:381-384.

22. Gaudreault J, Potvin D, Lavigne J, Lalonde RL. Truncated are under the curve as a measure of relative extent of bioavailability: Evaluation using experimental data and Monte Carlo Simulations. *Pharmaceutical Research,* 1998, 15:1621-1629.

23. Yusif et al., *Journal of the American Medical Association*. 1988, 260: 2259-22263.

24 . Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators, *New England Journal of Medicine*, 1991: 325. 293-302.

25. *The International Pharmacopoeia,* WHO, Geneva

26. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res*., 1995, 12: 413-420.

27. HHS/FDA Guidance for Industry: Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, August 2000. http://www.fda.gov/cder/guidance/index.htm

28. Yu LX, Amidon GL, Polli JE, et al. Biopharmaceutics Classification System: The scientific basis for biowaiver extensions. *Pharm. Res.* 2002, 19: 921-925.

29. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. *Pharm. Tech*., 1996, 20(6): 64-74.

30. Shah VP, Tsong Y, Sathe P, Liu JP. *In vitro* dissolution profile comparison-Statistics and Analysis of the Similarity factor, f_2. *Pharm. Res*. 1998, 15: 889-896.

31. Kasim NA, Whitehouse M, Ramachandran C et al. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Molecular Pharmaceutics*, 2004, 1: 85- 96.

32. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization model list of essential medicines according to the biopharmaceutics classification system. *Eur J. Pharmaceutics and Biopharm*. 2004, 58: 265-278.

33. Biowaiver monographs references: examples : *J.Pharm.Sci* 2004: 93(8): 1945-1956, *J.Pharm.Sci* 2005: 94(7): 1389-1395, *J.Pharm.Sci* 2005: 94(8): 16171-1617

34. *Proposal to waive* in vivo *bioequivalence requirements for the WHO Model List of Essential Medicines immediate release, solid oral dosage forms*, Working document QAS/04.109/Rev.1

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