WHO Technical Report Series, No. 937, 2006

Annex 7

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

1. Introduction

These guidelines are intended to provide recommendations to sponsors on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product.

The national health and drug regulatory authorities should ensure that all pharmaceutical products subject to their control conform to 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 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 the following:

— GMP;
— quality control specifications; and
— pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For 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 a wide range of pharmaceutical products the concepts and approaches covered by these guidelines will enable the national regulatory authority to decide whether a given multisource product can be approved. This guidance is generally applicable to orally administered multisource products, as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). For yet other classes of products, 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 beyond the scope of this document, and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of in vivo bioequivalence studies include pharmacokinetic studies, pharmacodynamic studies and comparative clinical trials. 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 often unnecessary and may be unethical. For these reasons the science of bioequivalence testing has been developed over the last 40 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent/alternative and bioequivalent. 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 comparison of dissolution profile of the multisource product with that of the comparator product, or dissolution studies, may be sufficient to provide indication of equivalence.

It should be noted that the concept of interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights (*1*).

2. Glossary

Some important terms used in these guidelines 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. Reliable measurements of drug concentrations at the site(s) of action are usually not possible. The substance in the 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. Based on pharmacokinetic and clinical considerations it is generally accepted 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 bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve (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.

Biopharmaceutics Classification System (BCS)

The 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 through in vivo equivalence testing.

comparator product

The comparator product is a pharmaceutical product with which the 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 have been established. The selection of the comparator product is usually made at the national level by the drug regulatory authority (see section 6.5.2).

dosage form

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

equivalence requirements

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

equivalence test

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

See *multisource pharmaceutical products.*

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 with the comparator in clinical practice.

in vitro equivalence test

An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the multisource product and the comparator product in three media: pH 1.2, pH 4.5 and pH 6.8.

in vitro quality control dissolution test

A dissolution test procedure identified in the pharmacopoeia, generally a one time point dissolution test for immediate-release products and a three or more time points dissolution test for modified release products.

multisource pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical alternatives

Products are pharmaceutical 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 to 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, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables 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, are 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 if they are to be considered interchangeable. Suitable test methods to assess equivalence are:

— comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (API) 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;
— comparative pharmacodynamic studies in humans;
— comparative clinical trials; and
— comparative in vitro tests.

The applicability of each of these four methods is discussed below. Detailed information is provided on conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the methods most often used 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 the characteristics of the API and the pharmaceutical product. Where an API produces measurable 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). Where an API does not produce measurable concentrations in an accessible biological fluid, comparative pharmacodynamic studies are an alternative method for documenting equivalence. In certain cases when it is not possible to determine the pharmacokinetic profile or to find suitable pharmacodynamic end-points, comparative clinical trials may be considered appropriate.

The 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 product are considered to be equivalent without the need for further documentation:

(a) when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product. Certain excipients (e.g. buffer, preservative and 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 (e.g. syrups, elixirs and tinctures), contain the API in the same molar concentration as the 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 API in the GI tract should be critically reviewed;
(c) when pharmaceutically equivalent products are in the form of powders for reconstitution as a solution and the resultant 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 API(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 their use 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 API(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 API(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 situations (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 concentrations comparable to those in the comparator product or, where applicable (i.e. (e) and (g)), that their use is not expected to affect the safety and/or efficacy of the product. In the event that this information cannot be provided by the applicant and the drug regulatory authority does not have access to the relevant 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 study required

Except for the cases discussed in section 4, these guidelines recommend that documentation of equivalence with the comparator product be required 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 (*2*). 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 bioinequivalence related to the API or its formulations (unrelated to dissolution problems);
- there is scientific evidence to suggest that polymorphs of API, the excipients and/or the pharmaceutical processes used in manufacturing could affect bioequivalence.

(b) Non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives).
(c) Modified-release pharmaceutical products designed to act systemically.[1]
(d) Fixed-combination products with systemic action, where at least one of the APIs requires an in vivo study (*3*).
(e) Non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal 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, measurement of the concentration of the API may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

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, pharmacodynamic and clinical studies are all clinical trials and should therefore 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*). Additional guidance for organizations performing in vivo bioequivalence studies is available from WHO (*5*).

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.

[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.

6.1.2 *Justification of human bioequivalence studies*

Most pharmacokinetic and pharmacodynamic equivalence 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 or benefits of the proposed human study be thoroughly considered and that the chosen design 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. The overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the API. Information about manufacturing procedures and data from tests performed on the product batch to be used in the study should establish that the product under investigation is of suitable quality.

6.1.3 *Selection of investigators*

The investigator(s) should have the appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigator(s) and the sponsor should draw up an agreement on the protocol, monitoring, auditing, standard operating procedures (SOP) and the allocation of trial-related responsibilities. The identity and duties of the individuals 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*

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or 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. Any change(s) required must be agreed on and signed by the investigator and sponsor, and appended as amendments, 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 (e.g. institutional review board, peer review committee, ethics

committee, drug regulatory authority), constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

A signed and dated study protocol together with the study report should be presented to 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 API for systemic exposure serve two purposes:

- as a surrogate for clinical proof of equivalence; and
- 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 far as possible. Test conditions should reduce variability within and between subjects. 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 alternative, well-established and statistically appropriate study design may 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. An adequate wash-out period should follow the administration of each product. The interval (wash-out period) between doses 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 should normally be more than five times the terminal half-life of the API. Consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under some other circumstances. For example, if the elimination rate of the product has high variability between subjects, the wash-out period may be longer to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of treatment during the second study period, blood samples are collected and assayed to determine the concentration of the API or metabolites. The minimum wash-out period should be at least seven days. The adequacy of the wash-out period can be estimated from the pre-dose concentration of the API and should be less than 5% of C_{max}.

It is currently not foreseen that there would be a need for blood samples to be collected for more than 72 hours.

6.2.1 *Alternative study designs for studies in patients*

For APIs that are very potent or too toxic to administer in the usual dose to healthy volunteers (e.g. because of the potential for serious adverse events, or the trial necessitates a high dose) it is recommended that the study be conducted using the API at a lower strength. However, if the pharmacokinetics are not proportional or if the solubility of the API is an issue, it will not be appropriate to extrapolate the bioequivalence results of the studies at lower strength to those at higher strengths. For APIs that show unacceptable pharmacological effects in volunteers, a multiple-dose, steady-state, cross-over study in patients or a parallel group design study in patients may be required. The alternative study design should be justified by the sponsor who should attempt to recruit 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 orally administered product with a long elimination half-life can be conducted provided an adequate wash-out period is used between admnistrations of the treatments. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally, the interval should not be less than five 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 the cross-over study is problematic, a pharmacokinetic bioequivalence study with a parallel design may be more appropriate.

For both cross-over and parallel-design studies, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2–3 days) of the pharmaceutical product and absorption of the API. Blood sampling up to 72 hours following administration 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 a parallel study design than for a 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 being studied 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 on either pharmacokinetic or pharmacodynamic end-points, although it is likely that using pharmacodynamic end-points would require a larger number of patients than pharmacokinetic end-points.

The dosage regimen used in multiple-dose studies 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 the pharmacokinetic profile after a single dose;
— extended-release dosage forms with a tendency to accumulation (in addition to a single-dose study).

In steady-state studies the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least three times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document for the attainment of a 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 variously known as controlled-release, prolonged-release and sustained-release products.

To establish the bioequivalence of 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 to provide more sensitive measurements of the release of API from the pharmaceutical product into the systemic circulation. Multiple-dose studies may need to be considered (in addition to a single-dose study) for extended-release dosage forms with a tendency to accumulate.

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

Coadministration of food with oral pharmaceutical products may influence drug bioavailability and also in certain cases pharmacokinetic bioequivalence. In addition to physiological changes in the gastrointestinal tract, food can affect the release of the API from the formulation. A concern with modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to “dose dumping”. This would most likely be manifested as a premature and abrupt rise in plasma concentration time profile. Therefore, a pharmacokinetic bioequivalence study under fed conditions is generally required for orally administered modified-release

pharmaceutical products. Omission of either the fed or fasting study should be justified by the applicant. A fed-state pharmacokinetic bioequivalence trial should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the medicine (see also section 6.4). A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should also take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and 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;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the reference product compatible with bioequivalence and with safety and efficacy;
- the need for the 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 recruited for the study should be estimated by considering the standards that must be met. It should be calculated by appropriate methods (see statistical analysis and acceptance criteria below). The number of subjects recruited should always be justified by 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 select a sufficient number of study subjects 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 or 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 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 these extra subjects will be assayed if not required for statistical analysis.

If the bioequivalence study was performed with the appropriate number of subjects but bioequivalence cannot be demonstrated because 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, provided this eventuality was anticipated and provided for in the study protocol. Combining data is acceptable only in the case that 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.

6.3.3 *Selection of subjects*

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, 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 fetus 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 administration of the first and last doses of the product under study.

Generally subjects should be between the ages of 18 and 55 years, and their weight should be within the normal range according to accepted life tables. The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability 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 API being investigated, e.g. an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been 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.

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should 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 any 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. In such cases, slow metabolizers will 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 of 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 cover exercise; diet; fluid intake; posture; and the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified time period before and during the study.

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

Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study drug is to be administered should be specified.

Medicines are usually given after an overnight fast of at least 10 hours, and participants are allowed free access to water. On the morning of the study no water is allowed during the hour prior to drug administration. The dose should be taken with a standard volume of water (usually 150–250 ml). Two hours after drug administration water is again permitted *ad libitum*. A standard meal is usually provided four hours after drug administration.

All meals should be standardized and the composition stated in the study protocol and report.

Some medicines are normally given with food to reduce gastrointestinal side-effects; in certain cases coadministration 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 state studies are also required in bioequivalence studies of modified release formulations. In these cases the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability (see 6.2.4). The test meal selected should take account of local custom and diet and should be consumed within 20 minutes. The product should be administered according to the protocol and within 30 minutes after the meal has been eaten.

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 multisource product, and the lot numbers and expiry dates of both multisource and comparator products should be stated.

Samples should ideally 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 API(s) of the comparator product should be close to the label claim, and the difference between two products should preferably be not 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 postmarketing monitoring schemes.

For some pharmaceutical products however, an innovator product cannot be identified; and in some cases no innovator product is 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 potentially 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. In principle, a national drug regulatory authority has the following options which are listed *in order of preference*:

(i) to choose the innovator product for which quality, safety and efficacy has been established if this product has been granted a national marketing authorization ("*nationally authorized innovator*"); or
(ii) to choose the WHO comparator product (for which marketing authorization has been granted, on the basis of quality, safety and efficacy) ("*WHO comparator product*"). The primary manufacturing site is indicated in the WHO comparator list (*6*), and the comparator is to be purchased in that country, or;
(iii) to choose the innovator product for which a marketing authorization has been granted in a well-regulated country (ICH or associated country) on the basis of quality, safety and efficacy ("*ICH et al. innovator*") and which is to be purchased from that market; or
(iv) in the case that no innovator product can be identified – within the context of (i)–(iii) above, the choice of the comparator must be made carefully and must be comprehensively justified by the applicant. The most important selection criteria in order of preference are:

— approval in ICH- and associated countries;
— "prequalified" by WHO;
— extensive documented use in clinical trials reported in peer-reviewed scientific journals; and
— long and unproblematic period of postmarket surveillance ("*well selected comparator*"). Additionally, "well selected comparators" must conform to compendial quality standards, where these exist.

Note: a product that has been approved based on comparison with a non-domestic comparator product may or may not be interchangeable with currently marketed domestic products.

In the context of regional harmonization efforts, it may be advantageous to establish a regional comparator product, for which quality, safety and efficacy has been established, in order to increase access to medicines.

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 must 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 (i.e. more than one dosage unit) 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. Alternatively, the application of area under the curve (AUC) truncated to 3 × median t_{max} of the comparator formulation would avoid problems of lack of assay sensitivity in many cases. In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety.

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 samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API 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 ($0 \rightarrow \text{infinity}$) can be accrued, but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form (see also 6.11.4).

6.6.3 *Sample fluids and their collection*

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the API. In most cases the API or its metabolites are measured in serum or plasma. If the API is excreted predominantly unchanged in the urine, urine can be sampled. The volume of each sample must be measured at the study centre, where possible immediately after collection, and included in the report. The number of samples should be suf-

ficient 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 been shown not to cause degradation of the analytes. This can be proven by analysing duplicate quality control 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.

The sample collection methodology must 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 rate (C_{max}, t_{max}) and extent (AUC) 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 sampling time point with a measurable concentration of the API in the individual formulation tested. 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 API (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 $AUC_{0-\infty} = AUC_{0–t} + C_{last}/ß$; C_{last} is the last measurable drug concentration and ß is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the drug at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

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

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

- AUCτ is AUC over one dosing interval (τ) at steady-state;
- C_{max};
- C_{min} is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage 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. The 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 (API) or metabolite) will be analysed in the samples.

In some situations it may be necessary to measure metabolite concentrations rather than those of the parent drug:

- The measurement of concentrations of therapeutically active metabolite is acceptable if the substance studied is a pro-drug.
- Measurement of a metabolite may be preferred when concentrations of the parent drug 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, API or metabolite, carries 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 both the consumer and producer risks change (*7*).

When measuring the active metabolites wash-out period and sampling times may need to be adjusted to enable adequate characterization of 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 API may be appropriate. Stereoselective assay is also preferred 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 to subjects in the fasted state, or if labelling restricts administration to subjects in the fed state, then the fed-state pharmacokinetic bioequivalence study becomes the preferred approach. The composition of the meal may depend on local diet and customs (see also section 6.4).

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 premature and abrupt rise in the plasma concentration time profile. A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should also take local diet and custom into consideration (see also section 6.2.4).

6.7 Quantification of active pharmaceutical ingredient

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 (*8*). Bioanalytical methods should meet the requirements of specificity, sensitivity, accuracy, precision and reproducibility. Knowledge of the stability of the API 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 analyses of biological samples in a pharmacokinetic study (*9*). Some of the important recommendations are:

- Validation comprises pre-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 a 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 will be used for 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 6–8 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 it still performs 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 from 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 the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report). Any modification of the method during the analysis of study samples will require adequate revalidation. The results of study sample determination should be given in the analytical report together with calibration and quality control 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 a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

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 (*10*). 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 analysis of variance (ANOVA). Usually the ANOVA model includes the formulation, period, sequence or carry-over and subject factors.

Parametric methods, i.e. those based on normal distribution theory, 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 within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance (*10*, *11*). 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.

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. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($T_{1/2}$) 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 to dealing with data containing outliers is to apply distribution-free (non-parametric), statistical methods (*12*).

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

Area under the curve-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 the 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 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} makes sense only 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 relevant ICH guideline (*13*) can be used in the preparation of the study report. The responsible investigator(s) should sign 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 ap-

plicant should submit a signed statement confirming that the test product is identical to 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 on 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 concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, including all calibration standards and quality control samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between drug application and blood sampling in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any 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 plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on those subjects who dropped out. The drop-outs 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 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-dose combination products*

If the pharmacokinetic bioequivalence of fixed-dose combination (FDC) products is assessed by in vivo studies the study design should follow the same general principles as described in previous sections. The multisource FDC product should be compared with the pharmaceutically equivalent comparator FDC product. In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator (*3*). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated on respect

to all compounds measured. Statistical analyses should be performed with pharmacokinetic data collected on 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. If a better formulation is developed over time by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition. Adjusting the strength to compensate with regard to sub- or suprabioavailability in comparison with the comparator product is beyond the scope of this document, as the prerequisite for pharmaceutical equivalence is not fullfilled.

6.11.3 *"Highly variable drugs"*

A "highly variable drug" has been defined as an API with a within-subject variability of ≥ 30% in terms of the ANOVA-CV (*14*). Moreover "highly variable drugs" are generally safe drugs with shallow dose–response curves. Proving the bioequivalence of medicinal 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.

- Some regulatory authorities permit the use of broadened bioequivalence limits provided there is adequate justification (*15*) 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.
- Some regulatory authorities 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 (*16–18*).
- Some regulatory authorities allow the following acceptance criteria: "Products are considered to be bioequivalent, if the 90% confidence interval of average ratios of AUC and C_{max} between test and reference products is within the acceptable range of 0.8–1.25 (*19*); if the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied:
  - — 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;

— the ratio of geometric least squares means of AUC and C_{max} between the multisource and comparator product are between 0.9 and 1.11; and
— dissolution rates of test and reference products are evaluated to be equivalent under all dissolution testing conditions (*19*).

This rule cannot be applied to slowly dissolving products from which less than 80% of a drug dissolves 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 (*19*).

- Some regulatory authorities do not allow for any adjustments (*20*).

The regulatory authority of the country should adopt one of these approaches prospectively to regulate the market authorization of highly variable pharmaceutical products.

6.11.4 *Application of truncated area under the curve 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 at low concentrations in plasma usually require sophisticated and expensive equipment to enable the API to be measured in the terminal portions of the plasma concentration versus time curve. When considering 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 the bioequivalence decision-making process (*21*, *22*). 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 four times t_{max} and the area extrapolated to infinity. The evidence suggests that for immediate-release formulations it is unnecessary to take blood samples beyond four times t_{max} (*23*). There are two important advantages to the use of truncated areas:

- more blood samples can be clustered around t_{max} to give greater precision in the estimation of both t_{max} and C_{max};
- high assay sensitivity to define the disposition phase is not required.

The applicability of the truncated AUC approach merits particular consideration in the following cases:

— 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
— for products of APIs 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 API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is 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 complicate 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 API and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity (see section 6.11.4 on truncated areas). Furthermore, pharmacodynamic bioequivalence studies in humans are required if measurements of API concentrations cannot be used as surrogate end-points 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 to performing pharmacodynamic bioequivalence studies. Pharmacodynamic bioequivalence studies may be therefore appropriate for pharmaceutical products administered topically and for 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 measuring pharmacodynamic drug responses.

- The response 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 product nor the comparator product should produce a maximal response in the course of the study, since it may be impossible to detect 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 by an instrument that produces and records the results of repeated measurements to provide a record

of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.

- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders 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 potential 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.

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

In studies in which continuous variables can 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 are measured, and parameters can be derived which describe the area under the effect–time curve, the maximum response and the time at which the maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle the same as those outlined for the analysis of 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 and should be justified on a case-by-case basis and defined in the protocol.

8. Clinical trials

In some instances (see example (e) in section 5.1, "In vivo studies") plasma concentration time–profile data are not suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic bioequivalence studies can be an appropriate tool for establishing equivalence, in others, this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters which can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between

two formulations. In cases when equivalence can be assessed by a pharmacokinetic bioequivalence study, this is preferred, because the analogous clinical trial would be less sensitive. Huge numbers of subjects are required to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study drug compared with placebo (*24*). Similarly it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of two formulations of the same API based on such end-points would require even greater numbers of subjects (*25*).

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 needed in pharmacokinetic bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic end-point has not yet evolved as extensively as for pharmacokinetic bioequivalence trials. However, some important items which need to be defined in the protocol can be identified.

- The target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity 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 should be set individually according to the therapeutic class and indication(s).
- The presently used statistical method is the confidence interval approach. The main concern is to rule out the possibility 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 end-points in the final comparative assessments.
- The 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 as 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 although the dissolution tests recommended in *The International Pharmacopoeia* (*26*) for quality control have been designed to be compatible with the biowaiver dissolution tests, they may not fulfil all the requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for quality control purposes in other pharmacopoeia do not generally 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

9.1.1 *Biopharmaceutics Classification System*

The Biopharmaceutics Classification System (BCS) is based on aqueous solubility and intestinal permeability of the drug substance. It classifies the 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 pharmaceutical product with these two properties of the API, takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into account (*27*). On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of solubility and permeability of the API, 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 (*28*). 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 1.2–6.8. 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 (*28*) suggested that the solubility should be measured over a pH range of 1.2–7.5. But successive scientific discussions and publications suggest that a pH range of 1.2–6.8 is more appropriate (*29*).

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 with an intravenous comparator dose. The initial recommendation in the BCS Guidance (*28*) suggested an absorption value of ≥ 90% as a prerequisite for classification as highly permeable. However, successive scientific discussions and scientific publications have suggested relaxing the criterion to 85% absorption for classifying an API as highly permeable (*29*). An acceptable alternative test method for permeability determination of the API could be in vivo intestinal perfusion in humans (i).

When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

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

(ii) in vivo or in situ intestinal perfusion using animal models; or
(iii) 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 neither method (ii) nor (iii) would be considered acceptable on a stand-alone basis. In these experiments high permeability is assessed with respect to the high permeability of a series of reference compounds with documented permeabilities and fraction absorbed values, including some for which fraction of dose absorbed is at least 85% (*29*).

9.1.2 *Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the Biopharmaceutics Classification System*

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% of the labelled amount of the drug substance dissolves in 15 minutes 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:

— pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

(See also section 9.2, dissolution profile comparison.)

9.1.2.2 *Rapidly dissolving*

A multisource product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolves in 30 minutes 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:

— pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

9.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

A biowaiver based on the BCS considers:

(a) the solubility and permeability of the API (see section 9.1);
(b) the similarity of the dissolution profiles 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 of, and clinical indications for, the API (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 reduction and assessment of excipients

The risk of reaching an inadequate 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 use in 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. by effects on gastrointestinal motility or interactions with transport processes), or which might lead to interactions that alter the pharmacokinetics of the API.

Evidence that each excipient present in the multisource product is well established and does not affect gastrointestinal motility or other processes affecting absorption, can be documented using the following information:

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 on the composition of drug products with marketing authorization is available on the web sites 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 decision on equivalence using a biowaiver based on the BCS.

Sub- and suprabioavailable products

A further consideration is the potential risk to public health and to 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 of sub-bioavailability.

The second negative outcome arises when the multisource product is suprabioavailable. 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 of

suprabioavailability. 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 the 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 measured under the same test conditions using an apparatus that conforms to the specifications in *The International Pharmacopoeia* using either the paddle method at 75 rpm or the basket method at 100 rpm at pH 1.2, 4.5 and 6.8 (*International Pharmacopoeia* 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, e.g. at 10, 15, 20, 30, 45 and 60 minutes. A minimum of 12 dosage units of each product (multisource and comparator) should be evaluated (*30*, *31*).

The dissolution profiles of the multisource and comparator products 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. A minimum of three time-points (zero excluded) is required for the calculation of f_2. 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:

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

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 (*30*, *31*).

If the comparator and multisource products are very rapidly dissolving, i.e. at least 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 comparison of dissolution profiles, 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 Biopharmaceutics Classification System according to the properties of active pharmaceutical ingredients*

The major application of BCS is to provide criteria for biowaiver of multisource products. Classification of APIs on the *WHO Model List of Essential Medicines* according to the WHO criteria described in this document are available (*32*). Further, a series of individual biowaiver monographs has been initiated (*33*). To date the BCS Guidance of the United States Department of Health and Human Services, Food and Drug Administration of the USA (HHS-FDA) recommends the biowaiver only for drug products containing Class 1 drugs (*28*). 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:

- BCS Class 3 drug products, if the multisource and comparator product are very rapidly dissolving (no less than 85% in 15 minutes at pH 1.2, 4.5 and 6.8); and
- BCS Class 2 weak acids if the API has a dose:solubility ratio of 250 ml or less at pH 6.8 and the multisource product is rapidly dissolving (no less than 85% in pH 6.8 in 30 minutes) 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 (*32*).

In summary, biowaivers for solid oral dosage forms based on BCS can be considered under the 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 (a–d) listed 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/or 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, some but not all 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 (i.e. the fraction absorbed is 85% or greater) 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 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 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, e.g. of surfactants, in the formulation. Further, if the C_{max} is critical to the therapeutic efficacy of the API, the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients may be deemed unacceptable.

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 proportions in the different strengths (e.g. a tablet of 50 mg strength has all the active and 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, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit), 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 in in vivo studies 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 strength studied. When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to that of the strength studied on a percentage released against time basis, the biowaiver procedure can be considered for the further strengths.

As in the case of biowaivers based on the BCS, a biowaiver based on dose-proportionality of formulations should be considered only 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 biowaivers based on the 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 measured 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 and 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 for the different strengths are similar.

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

9.3.3.2 *Delayed-release tablets and capsules*

For delayed-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 delayed-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profile, $f_2 > 50$, in the recommended test condition for delayed-release product, i.e. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8.

For delayed-release capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$) under the test conditions recommended for delayed-release products (see above) is sufficient for a biowaiver.

9.3.3.3 *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 the API, dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

9.3.3.4 *Extended-release tablets*

For extended-release tablets, when the multisource product is in the same dosage form, but in a different strength, 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 different 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 these guidelines comment primarily on registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following minor formulation or manufacturing changes after drug approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics.

Acknowledgements

The World Health Organization acknowledges with thanks the input of the following: International Pharmaceutical Federation/World Health Organization/Biopharmaceutics Classification System (FIP/WHO/BCS) Task Force members: Kamal K. Midha, Vinod P. Shah, Gordon Amidon, Dirk Barends, Jennifer Dressman, John Hubbard, Hans Junginger, Rabi Patnaik, James Polli and Salomon Stavchansky.

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