



The European Agency for the Evaluation of Medicinal Products  
*Human Medicines Evaluation Unit*

London, 17 December 1998  
CPMP/EWP/QWP/1401/98 Draft

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS  
(CPMP)**

**NOTE FOR GUIDANCE ON  
THE INVESTIGATION OF BIOAVAILABILITY AND  
BIOEQUIVALENCE**

<b>DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING PARTY</b>	December 1997- October 1998
<b>TRANSMISSION TO THE CPMP</b>	July 1998
<b>RELEASE FOR CONSULTATION</b>	December 1998
<b>DEADLINE FOR COMMENTS</b>	June 1999

7 Westferry Circus, Canary Wharf, London E14 4HB, UK  
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 85 51  
E-Mail: [mail@emea.eudra.org](mailto:mail@emea.eudra.org) <http://www.eudra.org/emea.html>

©EMEA 1998 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

## BACKGROUND INFORMATION

This Note for Guidance on 'investigation of bioavailability and bioequivalence' was first adopted by the CPMP in December 1991.

In the meantime, new developments have emerged in the field of pharmacokinetics, biopharmaceutics and statistics, and new issues have been raised in trying to apply the existing guideline during the assessment of medicinal products and namely concerning essential similarity domain (especially within the Mutual Recognition Procedure). An urgent revision of the existing guideline was therefore felt necessary. The CPMP, in October 1997, set up a 'Joint EWP/QWP group of experts on Pharmacokinetics issues' to undertake this task.

The 'Joint EWP/QWP experts group on Pharmacokinetics issues' has met six times. The review primarily concentrated on sections 3.5, 5.1 and 5.2 of the existing NfG (i.e. 'Reference and test product', 'Bioequivalence studies' and 'Exemption'), but a general review of the other sections was also undertaken. As a result, a revised guideline has been generated and substantial progress has been made by the group which has been acknowledged by the CPMP.

However, there were a number of issues which proved difficult for the CPMP to reach an agreement on. The most critical issues concern the approach of the exemption (or not) of bioequivalence studies and on which criteria to be met to qualify for exemption (i.e. section 5.1). It was recognised that there are difficulties in achieving harmonisation on waiving (or not) bioequivalence studies for immediate release products.

Moreover, the CPMP noted the recent judgement of the European Court of Justice in the "Generics" case (Case C-368/96). This judgement introduces a new definition of "essential similarity" which will have implications for the wording and interpretation of this guideline. This has not been taken into account in this current draft.

Despite the above mentioned difficulties, the CPMP has decided to release this 'draft' guideline for 6 months public consultation in order to gather external input from Academia and Industry in an attempt to resolve the outstanding issues and to achieve a satisfactory consensus on a final guideline.

# INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

## 1. INTRODUCTION

To exert an optimal therapeutic action an active substance should be delivered to the site of its action in an effective concentration for the desired period. To allow prediction of the therapeutic effect the performance of the pharmaceutical form containing the active substance should be reproducible. Several therapeutic misadventures in the past (digoxin, phenytoin, primidone) testify to the necessity of this reproducibility as a quality requirement. Thus the bioavailability (see definition) of an active substance from a pharmaceutical product should be known and be reproducible. This is especially the case if one product is to be substituted for another. In that case the product should show the same therapeutic effect in the clinical situation. It is generally cumbersome to assess this by clinical studies.

Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site of action and thus in an essentially similar effect, pharmacokinetic data instead of therapeutic results may be used to establish equivalence: bioequivalence (see definition).

It is the objective of this guidance to define, for products with a systemic effect, when bioavailability or bioequivalence studies are necessary and to formulate requirements for their design, conduct, and evaluation. This guideline should be read in conjunction with the Directive 75-318/EEC, as amended, and other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- Pharmacokinetic Studies in Man
- Modified Release Oral and Transdermal Dosage Forms: Section I (Pharmacokinetic and Clinical Evaluation)
- Modified Release Oral and Transdermal Dosage Forms: Section II (Quality)
- Investigation of Chiral Active Substances.
- Fixed Combination Medicinal Products
- Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents.
- The Investigation of Drug Interactions
- Development Pharmaceuticals
- Manufacture of the Finished Dosage Form
- Validation of analytical procedures: Definitions and Terminology (ICH topic Q2A)
- Validation of analytical procedures: Methodology (ICH topic Q2B)
- Structure and Content of Clinical Study Reports (ICH topic E3)
- Good Clinical Practice: Consolidated Guideline (ICH topic E6)
- General Considerations for Clinical Trials (ICH topic E8)
- Statistical Principles for Clinical Trials (ICH topic E9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Amendments to Commission Regulation on (EC) 542/95

For medicinal products not intended to be delivered into the general circulation the common systemic bioavailability approach cannot be applied. Under these conditions the (local) availability may be assessed, where necessary, by measurements quantitatively reflecting the presence of the active substance at the site of action using methods specially chosen for that combination of active substance and localisation (see section 5.1.8).

## 2. DEFINITIONS

Before defining bioavailability and related terminology some definitions pertaining to pharmaceutical forms are given:

### 2.1 Pharmaceutical equivalents

Medicinal products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

### 2.2 Pharmaceutical alternatives

Medicinal products are pharmaceutical alternatives if they contain the same therapeutic moiety but differ in chemical form of that moiety or in the dosage form or strength.

The therapeutic moiety may be used in the form of salts, esters, etc.

### 2.3 Bioavailability

Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

In the majority of cases substances are intended to exhibit a systemic therapeutic effect, and a more practical definition can then be given, taking into consideration that the substance in the general circulation is in exchange with the substance at the site of action:

- Bioavailability is understood to be the extent and the rate to which a substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation.

It may be useful to distinguish between the “absolute bioavailability” of a given pharmaceutical form as compared with that (100%) following intravenous administration (*e.g. oral solution vs. i.v.*), and the “relative bioavailability” as compared with another form administered by any route other than intravenous (*e.g. tablets vs. oral solution*).

### 2.4 Bioequivalents

Two medicinal products are bioequivalent if they are pharmaceutical equivalents or alternatives and if their bioavailabilities (rate and extent) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

### 2.5 Essentially similar products

A proprietary medicinal product will be regarded as essentially similar to another product if it has the same qualitative and quantitative composition in terms of active principles (substances), and the pharmaceutical form is the same and, where necessary, bioequivalence with the first product has been demonstrated by appropriate bioavailability studies. By extension, for immediate release products the concept of essentially similar also applies to different oral forms (*e.g. tablets and capsules*) with the same active substance (see "The rules governing medicinal products in the European Community", Notice to Applicants, Vol. 2A).

An essentially similar product is intended to be substituted for an innovator product. An 'innovator' product is a medicinal product authorised and marketed on the basis of a full dossier *i.e.* including chemical, biological, pharmaceutical, pharmacological–toxicological and clinical data.

## 2.6 Therapeutic equivalents

A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically shows the same efficacy and safety as that product, whose efficacy and safety has been established.

In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products which are pharmaceutical equivalents or alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy. However, in some cases where different rates of absorption are observed the products - though not bioequivalent - can be judged therapeutically equivalent if the differences in absorption rate are not of therapeutic relevance.

For other considerations on this subject reference is made to an annex to this guideline (Appendix I).

## 3. DESIGN AND CONDUCT OF STUDIES

In the following sections, requirements for the design and conduct of bioequivalence studies are formulated. It is assumed that the applicant is familiar with pharmacokinetic theories underlying bioavailability studies. The design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question. For the pharmacokinetic basis of these studies reference is made to the recommendation "Pharmacokinetic studies in man". The design and conduct of the study should follow EU-regulations on Good Clinical Practice, including reference to an Ethics Committee.

### 3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. A crossover design, which can remove the inter-subject variability from the comparison of average bioequivalence between formulations, may be considered. Other designs may be chosen in specific situations, but should be fully justified in the protocol and in the final study report. The subjects should be allocated to treatment sequences in a randomised order.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required:

- a) if problems of sensitivity preclude sufficiently precise plasma concentration measurement after single dose;
- b) if the intra-individual variability in the plasma concentrations or disposition rate is inherently large;
- c) in the case of dose- or time-dependent pharmacokinetics;
- d) in the case of modified release products (in addition to single dose studies).

In such steady-state studies the administration scheme should follow the usual dosage recommendations.

The number of subjects required should be determined by the error variance associated with each of the pharmacokinetic parameters of primary interest (e.g. AUC,  $C_{max}$ ) as estimated, from a pilot experiment, from previous studies or from published data, by the coverage probability of the confidence interval for relative bioavailability, by the expected deviation from the reference product compatible with bioequivalence and by the required power. The clinical and analytical standards imposed may also influence the statistical determined number of subjects. However, the minimum number of subjects should not be smaller than 12.

Subsequent treatments should be separated by periods long enough to eliminate the previous dose (wash-out period).

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

The sampling schedule should be planned to provide an adequate estimation of C<sub>max</sub> and to cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of absorption; this is generally achieved if the AUC derived from measurements is at least 80% of the individual AUC extrapolated to infinity.

In a steady-state bioequivalence study, when the circadian rhythm is known to have an influence on bioavailability, sampling schedule should be carried out over a full 24 hours cycle.

If bioequivalence is to be established on a pharmacodynamic effect, routinely a double blind study should be performed including test, reference and placebo treatments.

## **3.2 Subjects**

### **3.2.1 Selection of subjects**

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should be performed with healthy volunteers. The inclusion /exclusion criteria should be clearly stated in the protocol.

Subjects could belong to both sexes; however, the risk to women of childbearing potential should be considered on an individual basis.

In general, subjects should be between 18 - 55 years old and of weight within the normal range according to accepted life tables. They should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile special medical investigations may have to be carried out before, during and after the completion of the study. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included (less than 10 cigarettes per day) they should be identified as such and the consequences for the study results should be discussed.

If the purpose of the bioequivalence study is to address specific questions such as investigation of differences in bioavailability in different subsets of the population or drug-drug interactions the selection criteria and the statistical analysis should be adjusted accordingly.

### **3.2.2 Standardisation of the study**

The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Therefore, standardisation of the diet, fluid intake, exercise and posture is recommended. Subjects should preferably be fasting at least during the night prior to administration of the products. If the reference product is administered with food, subjects should take a standard meal at a specified time before the treatment. The time of day for ingestion should be specified and as fluid intake may profoundly influence gastric passage, the volume of fluid (at least 150ml) should be constant. All meals and fluids taken after the treatment should also be standardised in regard to composition and time of administration. The subjects should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastro-intestinal, liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices). As the bioavailability of an active substance from a dosage

form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

### **3.2.3 Inclusion of patients**

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients instead under suitable precautions and supervision. In this case the applicant should justify the alternative.

### **3.2.4 Genetic phenotyping**

Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

## **3.3 Characteristics to be investigated**

In most cases evaluation of bioequivalence will be based upon the measured concentrations of the parent compound. This may be impossible if (1) the concentration of the parent compound is too low to accurately measure in the biological matrix (e.g. major difficulty in analytical method, product unstable in the biological matrix) thus giving rise to significant variability or if (2) the half-life of the parent compound is too short to derive any meaningful pharmacokinetic parameters. In this situation, a major biotransformation product should be used provided it reflects the bioavailability of the active substance. Measurement of the concentrations of an active biotransformation product is also essential if the parent compound is a prodrug.

Where the biotransformation product is formed predominantly by a saturable first pass metabolism, concentration-time curves of the metabolite cannot be used to assess bioavailability.

If urinary excretion (rate) is measured the product determined should represent a major fraction of the dose and the excretion rate should be considered to parallel plasma concentrations of the active substance.

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

If pharmacodynamic effects are used as characteristics the measurements should provide a sufficiently detailed time course, the initial values in each period should be comparable and the complete effect curve should remain below the maximum physiological response. Specificity, accuracy and reproducibility of the measurements should be sufficient. The non-linear character of the dose/response relationship should be taken into account and base line measurements should be subtracted before data analysis.

### 3.4 Chemical analysis

The bioanalytical methods used to determine the active principle and/or its biotransformation product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) concentration in a specific biological matrix. The characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are (1) stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage (2) specificity (3) accuracy (4) sensitivity (5) precision and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase in which the assay is developed to comply with the six characteristics listed above and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the biostudy mainly evaluating stability, accuracy and reproducibility. In addition, it is necessary to validate the method of processing and handling the biological samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs). All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed. Any modification of the bioanalytical method before and during analysis of study specimens requires adequate revalidation; all modifications should be reported and the scope of revalidation justified.

For the validation of analytical methods reference can be made to the relevant ICH guidelines 'Validation of analytical procedures: Definitions and Terminology' and 'Validation of Analytical Procedures: Methodology'.

Attention should be given to the requirements of the note for guidance on the "Investigation of Chiral Active Substances" as far as relevant for bioavailability and bioequivalence studies.

### 3.5 Reference and test product

Test products are normally compared with the corresponding form of a well-established 'innovator' medicinal product (reference product). The choice of reference product should be justified by the applicant.

For an abridged application claiming essential similarity to a reference product, application to numerous Member States based on bioequivalence with a reference product from one Member State can be made. However, the application can only be considered acceptable if the reference products have the same manufacturer (or its subsidiaries) and if the dissolution profiles of the reference products are similar on discriminatory dissolution testing (Appendix IV). Concerned Member States may request additional information from the first Member State on the reference product, namely on the composition (qualitative and quantitative) in excipients and information on the manufacturing process and finished product specification. Where the dissolution profiles are dissimilar and bioequivalence studies are required, they should be carried out using, as reference product, the product registered in the concerned Member State.

It should be remembered that the development of the test product should always take into account the Note for Guidance "Development Pharmaceuticals".

The test products used in the biostudy must be prepared in accordance with GMP-rules. Batch control results of the test product should be reported. The test product must originate from a batch of at least 100000 units or 1/10 of a full production batch whichever is larger. This

should be prepared by a manufacturing process which meaningfully simulates that which will be used in production; in case of production batch smaller than 100000 units, a full production batch will be required.

If the product is subjected to further scale-up, samples of the product from production batches should be compared with those of the test batch, and should show similar 'in vitro' dissolution profiles (see Appendix IV) when employing suitably discriminatory dissolution test conditions. The study sponsor will have to retain a sufficient number of product samples for one year in excess of the accepted shelf life to allow retesting, if-requested by the authorities.

### **3.6 Data analysis**

The primary concern in bioequivalence assessment is to limit the risk of erroneously accepting bioequivalence which should not exceed the nominal risk of 5%, and to try to minimise the risk of erroneously rejecting bioequivalence.

#### **3.6.1 Statistical analysis**

The statistical method for testing bioequivalence is based upon the 90% confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. This method is equivalent to the corresponding two one-sided test procedure with the null hypothesis of bioinequivalence at the 5% significance level. The statistical analysis (e.g. anova) should take into account sources of variation that can be reasonably assumed to have an effect on the response

The validity of the assumptions underlying the statistical analysis (e.g. additivity, normality) may often be improved by transforming the raw data prior to analysis, preferably using a logarithmic transformation.

This is suggested for the pharmacokinetic parameters that derived from measures of concentration e.g. AUC,  $C_{max}$ , etc.

The statistical methods for  $t_{max}$  should be non-parametric. For all pharmacokinetic parameters of interest in addition to the appropriate 90% confidence intervals for the comparison of the two formulations, summary statistics such as median, minimum and maximum should be given

#### **3.6.2 Handling deviations from the study plan**

The method of analysis should be planned in the protocol. The protocol should also specify methods for handling drop-outs and for identifying biologically implausible outliers. Post hoc exclusion of outliers is not generally accepted. If modelling assumptions made in the protocol (e.g. for extrapolating AUC to infinity) turn out to be invalid, a revised analysis in addition to the planned analysis (if this is feasible) should be presented and discussed.

#### **3.6.3 A remark on individual and population bioequivalence**

To date, most bioequivalence studies are designed to evaluate average bioequivalence. Experience with population and individual bioequivalence studies is limited. Therefore, no specific recommendation is given on this matter. However, studies with replicate design may be helpful for substances with highly variable absorption.

### **3.7 'In vitro' dissolution complementary to a bioequivalence study**

The results of "in vitro" dissolution tests, obtained with the batches of test and reference products that were used in the bioequivalence study should be reported.

These results should be reported as profiles of amount dissolved versus time for individual dosage units.

The specifications for the "in vitro" dissolution of the product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product.

For immediate release products, if the dissolution profile of the test product is dissimilar compared to that of the reference product and the in vivo data remain acceptable, the dissolution test method should be re-evaluated and optimised. In case that no discriminatory test method can be developed which reflects in vivo bioequivalence a different dissolution specification for the test product could be set.

### **3.8 Reporting of results**

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP-rules and related EU and ICH E3 guidelines. This implies that the authenticity of the whole of the report is attested by the signature of the study monitor. The responsible investigator (s) should sign for their respective sections of the report.

Names and affiliations of the responsible investigator (s), site of the study and period of its execution should be stated. The names and batch numbers of the products used in the study as well as the composition(s) of the test product(s) should be given. In addition, the applicant should submit a signed statement confirming that the test product is the same as the one which is submitted for marketing authorisation.

All results should be clearly presented and should include data from subjects who eventually drop-out. Drop-out of subjects and withdrawals should be fully documented and accounted for. The method used to derive the pharmacokinetic parameters from the raw data should be specified. The data used to estimate AUC should be reported. If pharmacokinetic models are used to evaluate the parameters the model and computing procedure used should be justified. Deletion of data should be justified.

All individual subject data should be given and individual plasma concentration/time curves presented on linear/linear and log/linear scale. The analytical report should include the results for all standard and quality control samples as well. A representative number of chromatograms or other raw data should be included covering the whole concentration range for all, standard and quality control samples as well as the specimens analysed. The analytical validation report should be submitted as well.

The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated.

## **4. APPLICATIONS FOR PRODUCTS CONTAINING NEW ACTIVE SUBSTANCES**

### **4.1 Bioavailability**

In the case of new active substances (new chemical entities) intended for systemic action the pharmacokinetic characterisation will have to include the determination of the systemic availability of the substance in its intended pharmaceutical form in comparison with intravenous administration. If this is not possible the bioavailability relative to a suitable oral solution or standardised suspension should be determined. In the case of a prodrug the intravenous reference solution should preferably be the therapeutic moiety.

## 4.2 Bioequivalence

The dosage recommendations for the market form of a new active substance should be validated by a comparative bioavailability study against the forms used in the clinical trials, especially those used in the dose finding studies, unless its absence can be justified by satisfactory in vitro data.

## 5. APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES

### 5.1 Bioequivalence studies

Bioequivalence is required if a product is intended to be substituted for an approved medicinal product.

Requirements for the demonstration of bioequivalence may vary with this type of product.

#### 5.1.1 Oral Immediate Release Forms with systemic action

Bioequivalence studies should be performed for all immediate release products intended for systemic action unless, considering all of the following criteria, the applicant can establish that in vitro data are sufficient to ensure bioequivalence.

As an example in vitro data alone would be acceptable if all of the following criteria are fulfilled, as follows:

- a. The active substance is known not to require special precautions with respect to precision and accuracy of dosing, e.g., it does not have a narrow therapeutic range;
- b. The pharmacokinetics are characterized by a pre-systemic elimination /first pass metabolism less than 70%; and linear pharmacokinetics within the therapeutic range ;
- c. The drug is highly water soluble, i.e. the amount contained in the highest strength is dissolved in 250 ml of each of three pharmacopoeial buffers within the range of pH 1 - 8 at 37 °C (preferably at or about pH 1.0, 4.6, 6.8)
- d. The drug is highly permeable in the intestine, i.e. its extent of absorption is greater than 80%. Permeability of a drug substance can be determined by different methods, such as, in vivo (e.g. intestinal perfusion in humans, human pharmacokinetic/mass balance studies), in vitro (e.g. CaCo2 cell cultures) and in situ (e.g. intestinal perfusion in animals) The choice of the method has to be justified by the applicant in terms of the ability to predict the rate and extent of absorption in humans. Stability of the drug should be documented under various conditions typical for the gastrointestinal tract.
- e. the excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected;

In case an active substance qualifies for exemption, the excipients comply with criterion e) above, the method of manufacture of the finished product in relation with critical physicochemical properties of the active substance (e.g. particle size, polymorphism) should be adequately addressed and documented in the development pharmaceuticals section of the dossier.

#### 5.1.2 Oral solutions

If the product is an aqueous oral solution at time of administration containing the active substance in the same concentration and form as a currently approved medicinal product, not

containing excipients that may affect gastrointestinal transit or absorption of the active substance, then a bioequivalence study is not required.

In those cases where an oral solution has to be tested against a solid dosage form (e.g. an oral solution is formulated to be equivalent to an existing tablet), a comparative bioavailability study will be required unless an exemption can be justified (see 5.1.1)

### **5.1.3 Non-Oral Immediate Release forms with systemic action**

In general bioequivalence studies are required.

### **5.1.4 Modified Release dosage forms**

Requirements for bioequivalence studies in accordance with specific guideline (see *specific Note for Guidance*).

### **5.1.5 Fixed combinations products**

Combination products should be assessed with respect to the bioavailability and bioequivalence of individual active substances either separately or as an existing combination.

### **5.1.6 Parenteral formulations**

The applicant is not required to submit a bioequivalence study if the product is to be administered as an intravenous solution containing the active ingredient in the same concentration as the currently authorised product.

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, the product must be the same type of solution (aqueous or oily), contain the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved for this exemption to apply.

### **5.1.7 Gases**

If the product is a gas for inhalation a bioequivalence study is not required.

### **5.1.8 Locally applied products**

For products for local use (after oral, nasal, ocular, dermal, rectal, vaginal, *etc.*) administration intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required (see specific Note for Guidance)

## **5.2 In Vitro Dissolution**

Dissolution studies are required either as complementary (see 3.7) or surrogate to bioequivalence studies and must follow the guidance as laid out in Appendix IV. In the latter case similarity of dissolution profiles between test product and reference product based on discriminatory tests should be demonstrated (see Appendix IV)

## **5.3 Variations**

If a product has been reformulated from the formulation originally approved or the manufacturing method has been modified by the manufacturer in ways that could be considered to impact on the bioavailability, a bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per 5.1.1, or on whether an acceptable in vivo/in vitro correlation has been established.

In cases where the bioavailability of the original product has been investigated and an acceptable correlation between in vivo performance and in vitro dissolution rate has been established, the requirements for bioequivalence can be waived if the dissolution rate in vitro of

the new product is similar with that of the already approved medicinal product under the same test conditions as used to establish the correlation. In all other cases bioequivalence studies have to be performed.

For variations of the innovator's product the reference product for use in bioequivalence and dissolution studies is usually that authorised under the current formula, manufacturing method, packaging etc. and this is tested against product manufactured in line with the proposed changes.

When variations to an essentially similar product is made the reference product for the bioequivalence study should be the innovator's product.

#### **5.4 Dose proportionality in oral dosage forms**

If a new application concerns several strengths of the active substance only one bioequivalence study with the highest strength is necessary (unless a lower strength is chosen for reasons of safety) provided that the pharmaceutical products are manufactured by the same manufacturer, at the same manufacturing site and all of the following conditions hold:

- pharmacokinetics have shown to be linear over the therapeutic dose range;
- the qualitative composition of the different strengths is the same;
- the ratio between active substance and the excipients is the same, or, in the case of preparations containing a low concentration of the active substance, the ratio between the excipients is the same;
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

If a new strength is applied for on the basis of an already approved medicinal product, and all of the stated conditions hold then a bioequivalence study is not necessary.

#### **5.5 Suprabioavailability**

If suprabioavailability is found, i.e. if the new product displays a bioavailability appreciably larger than the approved product, reformulation to a lower dosage strength should be performed. The biopharmaceutical development should be reported and a final comparative bioavailability study of the reformulated new product with the old approved product should be submitted.

In case reformulation is not carried out the dosage recommendations for the suprabioavailable product will have to be supported by clinical studies if different from the reference product. Such a pharmaceutical product should not be accepted as therapeutic equivalent to the existing reference product and if marketing authorisation is obtained the new product may be considered as a new reference product.

To avoid confusion for both prescribers and patients, it is recommended that the name of the suprabioavailable product precludes confusion with the older approved product.

Suprabioavailable products cannot claim "essential similarity" (see section 2.5) with the innovator product.

## APPENDIX I

### Therapeutic Equivalents

Therapeutic equivalents contain the same active substance or therapeutic moiety and, when administered clinically, show the same efficacy/safety as the medicinal product whose efficacy and safety are established (cf. 2.6).

Accordingly, therapeutically equivalent products refer to products which are identical, similar or related to “innovator” medicinal products. Related products cover pharmaceutical alternatives, of which differences from pharmaceutical equivalents with respect to the dosage form (i.a), the chemical form (i.b), the strength (ii.) are considered to be medically meaningless.

- i) Generally, therapeutic equivalents consist of Bioequivalent forms:
  - either pharmaceutical equivalents (essentially similar medicinal products),
  - or, sometimes, pharmaceutical alternatives differing in:
    - a) The dosage form (e.g. capsules v. tablets);
    - b) Other chemical forms (e.g. the salt or ester) of the same therapeutic moiety, provided that evidence is supplied that such differences do not induce changes in pharmacokinetics, pharmacodynamics and/or in toxicity which could be clinically meaningful (i.e. theophylline and aminophylline).
- ii) Therapeutic equivalence may also include pharmaceutical equivalents or alternatives showing suprabioavailability if a comparative bioavailability study has shown that the product in question after adjustment in dosage displays the same bioavailability as the corresponding innovator product.

## APPENDIX II

### Explanation of the symbols in paragraph 3.3

<b>C<sub>max</sub>:</b>	maximal plasma concentration;
<b>C<sub>min</sub>:</b>	minimal plasma concentration;
<b>C<sub>av</sub>:</b>	average plasma concentration;
<b>t<sub>max</sub>:</b>	time passed since administration at which the plasma concentration maximum occurs;
<b>AUC<sub>t</sub>:</b>	area under the plasma concentration curve from administration to time t.
<b>AUC<sub>∞</sub>:</b>	AUC extrapolated to infinite time;
<b>AUC<sub>t</sub>:</b>	AUC during a dosage interval in steady state;
<b>MRT:</b>	mean residence time;
<b>Ae<sub>t</sub>:</b>	cumulative urinary excretion from administration until time t;
<b>Ae<sub>∞</sub></b>	cumulative urinary excretion extrapolated to infinite time;
<b>dAe/dt:</b>	urinary excretion rate;
<b>t<sub>1/2</sub>:</b>	plasma concentration half-life;
<b>Fluctuation:</b>	$(C_{\max} - C_{\min})/C_{\text{av}}$ or $(C_{\max} - C_{\min})/C_{\max}$

## APPENDIX III

### Acceptance criteria for Bioequivalence Studies

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

In studies to determine average bioequivalence the acceptance ranges for the main characteristics are:

#### **AUC-ratio**

The 90% confidence interval for this measure of relative bioavailability should lie within an *acceptance* range of 0.80-1.25. In case of an especially narrow therapeutic range the acceptance range may need to be tightened.

In rare cases (e.g. highly variable drugs) a wider acceptance range may be acceptable if it is based on sound clinical justification.

#### **C<sub>max</sub>-ratio**

This measure of relative bioavailability may be more variable than e.g. the AUC-ratio, and a wider acceptance range may be acceptable. The range used should be justified in the protocol taking into account safety and efficacy considerations.

#### **t<sub>max</sub> – diff**

Statistical evaluation of t<sub>max</sub> only makes sense if there is a clinically relevant claim for rapid release or action or signs for a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically determined range.

#### **Others**

For other (see 3.3) pharmacokinetic parameters (e.g. C<sub>min</sub>, Fluctuation, t<sub>1/2</sub>, etc) considerations analogous to those for AUC, C<sub>max</sub> or t<sub>max</sub> apply.

## APPENDIX IV

### Dissolution testing

A medicinal product is composed of drug substance and excipients and the proportion between them, the type of excipients and the manufacturing method of the final product are chosen based on both the content, the physicochemical and the bulk properties of the drug and on its absorption properties. Taken as a whole this gives each product certain dissolution characteristics.

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, a dissolution test can be used to support the bioavailability of a new drug product, the bioequivalence of an essentially similar product or variations.

Therefore, dissolution studies can serve several purposes:

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specification for routine quality control.
- To be used as a tool in quality control to demonstrate consistency in manufacture.
- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.
- To compare reference products from different Member States.
- To help to ascertain similarity between different formulations of a drug substance (variations and new, essentially similar products included) and the reference medicinal product.

The test methodology should be in accordance with compendial requirements unless shown to be unsatisfactory. Alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo.

If a drug is considered highly soluble it is reasonable to expect that it will not cause any bioavailability problems if besides the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration. A bioequivalence study may in those situations be waived based on no case history of bioavailability problems and similarity of dissolution profiles which are based on discriminatory testing, provided that the other exemption criteria in 5.1.1 are met. The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH range 1-6.8; in cases where it is considered necessary pH range 1-8 )

In the case of a drug or excipients that is sensitive to pH, profiles from only two buffer systems are required.

If a drug is considered to have a low solubility and a high permeability the rate limiting step for absorption may be drug dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the drug. In those cases a variety of test conditions is recommended and adequate samplings should be performed until either 90% of the drug is dissolved or an asymptote is reached. Knowledge of dissolution properties

under different conditions e.g. pH, agitation ionic strength, surfactants, viscosity, osmotic pressure is important since the behaviour of the solid system in vivo may be critical for the drug dissolution independent of the physico-chemical properties of the active substance. An appropriate experimental statistical design may be used to investigate the critical parameters and for the optimisation of such conditions.

The similarity of the profiles may be compared by model-independent or model-dependent methods e.g. by linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor e.g. the one defined below:

$$f_2 = 50 \cdot \log \left( \frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [\bar{R}(t) - \bar{T}(t)]^2}{n}}} \right)$$

In this equation  $f_2$  is the similarity factor,  $n$  is the number of time points,  $R(t)$  is the mean percent drug dissolved of e.g. a reference product, and  $T(t)$  is the mean percent drug dissolved of e.g. a test product.

The evaluation of similarity is based on the conditions of

- A minimum of three time points
- 12 individual values for every time point
- not more than one mean value of > 85% dissolved
- that the standard deviation of the mean should be less than 10% from second to last time point.

An  $f_2$  value between 50 and 100 suggests that the two dissolution profiles are similar. In cases where more than 85% of the drug are dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.