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NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

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Any comments should be sent to the EMEA, EWP Secretariat (Fax No. 44-20-74188613) before the end of March 2001.

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INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

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1 INTRODUCTION

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised**.**

In the past, several therapeutic misadventures related to differences in bioavailability (e.g. digoxin, phenytoin, primidone) testify to the necessity of testing the performance of dosage forms in delivering the active substance to the systemic circulation and thereby to the site of action. Thus the bioavailability of an active substance from a pharmaceutical product should be known and reproducible. This is especially the case if one product containing one active substance is to be used instead of its innovator product. 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.

Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative use between the innovator and any essentially similar medicinal product. 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.

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. The possibility of using *in vitro* instead of *in vivo* studies with pharmacokinetic end points is also envisaged.

This guideline should be read in conjunction with 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
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- Manufacture of the Finished Dosage Form
- Validation of analytical procedures: Definitions and Terminology (ICH topic Q2A)
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- Structure and Content of Clinical Study Reports (ICH topic E3)
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- Statistical Principles for Clinical Trials (ICH topic B9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Amendments to Commission Regulation on (EC) 542/95
- Common Technical Document (ICH topic M4)

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). In this case, as well as in others, alternative methods may be required such as studies using pharmacodynamic end points. Furthermore, where specific requirements for different types of products are needed, the appropriate exceptions are mentioned therein.

This Note for Guidance does not explicitly apply to biological products.

2 DEFINITIONS

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

2.1 Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent 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 active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

2.3 Bioavailability

Bioavailability means the rate and extent to which the active substance or active 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 active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non intravenous route (e.g. tablets vs. oral solution).

2.4 Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities 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.

Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.

2.5 Essentially similar products

The current EU definition for essentially similar products is as follows (see "The rules governing medicinal products in the European Union", Notice to Applicants, Vol. 2A in accordance with the December 1998 European Court of Justice ruling in the “Generics” case):

“A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy”.

By extension, it is generally considered that for immediate release products the concept of essential similarity also applies to different oral forms (tablets and capsules) with the same active substance.

The need for a comparative bioavailability study to demonstrate bioequivalence is identified under 5.1. Concerns about differences in essentially similar medicinal products lie on the use of different excipients and methods of manufacture that ultimately might have an influence on safety and efficacy. A bioequivalence study is the widely accepted means of demonstrating that these differences have no impact on the performance of the formulation in promoting absorption in the case of immediate release dosage forms. It is desirable that excipients must be devoid of any effect or their safe use is ensured by appropriate warning in the package label – see guideline on excipients in the label and package leaflet: “The Rules Governing Medicinal Products in the European Union”, 1998, Vol. 3B, - and not interfere with either the release or the absorption process.

An essentially similar product can be used instead of its 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. A 'Reference Product' must be an 'innovator' product (see 3.5).

2.6 Therapeutic equivalence

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 pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients. (see 2.5).

However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant may be necessary.

3 DESIGN AND CONDUCT OF STUDIES

In the following sections, requirements for the design and conduct of bioavailability or 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.

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. The following sections apply mainly to bioequivalence studies. Since bioavailability studies are comparative in nature, the contents of the following sections apply to these studies as well, with the necessary adaptations in accordance with the aim of each specific study. Where necessary, specific guidance concerning bioavailability studies will be given.

The methodology of bioequivalence studies can be used to assess differences in the pharmacokinetic parameters in pharmacokinetic studies such as drug-drug or food–drug interactions or to assess differences in subsets of the population. In this case the relevant guidelines should be followed and the selection of subjects, the design and the statistical analysis should be adjusted accordingly.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is often considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound alternative well-established designs could be considered such as parallel design for very long half-life substances and replicate designs for substances with highly variable disposition.

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

- are required, e.g. in the case of
  - dose- or time-dependent pharmacokinetics (mainly for bioavailability studies),
  - modified release products (in addition to single dose investigations),
- or can be considered, e.g.
  - if problems of sensitivity preclude sufficiently precise plasma concentration measurements after single dose administration.
  - if the intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single dose study.

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

The number of subjects required is determined by

a) the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data,

b) the significance level desired,

c) the expected deviation from the reference product compatible with bioequivalence and

d) the required power.

The clinical and analytical standards imposed may also influence the statistically determined number of subjects. However, generally the minimum number of subjects should be not smaller than 12 unless justified.

Subsequent treatments should be separated by adequate wash out periods. In steady-state studies wash out of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life).

The sampling schedule should be planned to provide an adequate estimation of C_{max} 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 AUC extrapolated to infinity**.** If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

In order to study bioavailability under steady-state conditions when differences between morning and evening or nightly dosing are known, (e.g. if it is known that the circadian rhythm is known to have an influence on bioavailability), sampling should be carried out over a full 24 hours cycle.

For drugs with a long half-life, relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of the absorption process.

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 normally 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 normal values for the Body Mass Index. 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.

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 Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake the study should be designed accordingly.

The time of day for ingestion should be specified and as fluid intake may profoundly influence gastric passage, the volume of fluid (at least 150 ml) should be constant. All meals and fluids taken after the treatment should also be standardised in regard to composition and time of administration during the sampling period. 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, gastrointestinal, liver or renal function (e.g.

alcoholic or xanthine-containing beverages or certain fruit juices). As the bioavailability of an active moiety 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 should be considered for exploratory bioavailability studies and all studies using parallel group design. It may be considered as well in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question.

3.3 Characteristics to be investigated

In most cases evaluation of bioequivalence will be based upon the measured concentrations of the parent compound. In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Such situations include cases where the use of a metabolite may be advantageous to determine the extent of drug input, e.g. if the concentration of the active substance is too low to be accurately measured in the biological matrix (e.g. major difficulty in analytical method, product unstable in the biological matrix or half-life of the parent compound too short) thus giving rise to significant variability.

Bioequivalence determinations based on metabolites should be justified in each case bearing in mind that the aim of a bioequivalence study is intended to compare the *in vivo* performance of test and reference products. In particular if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations.

In bioavailability studies, the shape of and the area under the plasma concentration *versus* time curves or the cumulative renal excretion and excretion rate are mostly used to assess extent and rate of absorption. The use of urine excretion data may be advantageous in determining the extent of drug input but has to be justified when used to estimate the 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_∞, C_{max}, t_{max}, Ae_t, Ae_∞, or any other justifiable characteristics (cf. Appendix I). 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_τ, C_{max}, C_{min} and fluctuation should be provided.

The exclusive use of modelled characteristics is not recommended.

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 corrections should be considered during data analysis.

3.4 Chemical analysis

The bioanalytical methods used to determine the active moiety 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 stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage; (2) specificity; (3) accuracy; (4) precision (5) limit of quantification and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase in which the compliance of the assay with the six characteristics listed above is verified and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the biostudy mainly in order to confirm the stability, accuracy and precision.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run. A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples. 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 (S0Ps). 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.

According to the requirements of the note for guidance on the "Investigation of Chiral Active Substances", bioequivalence studies supporting applications for essentially similar medicinal products containing chiral active substances should be based upon enantiomeric bio-analytical methods umless (1) both products contain the same stable single enantiomer; (2) both products contain the racemate and both enantiomers show linear pharmacokinetics.

3.5 Reference and test product

Test products are normally compared with the corresponding dosage form of an innovator (see 2.5) 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.

Such an application can be considered acceptable unless there is a significant difference between the reference products originating from the same manufacturer (or its subsidiaries), in terms of the qualitative and quantitative composition in excipients. Concerned Member States may request information from the first Member State on the reference product, namely on the composition, manufacturing process and finished product specification.

Where additional bioequivalence studies are required, they should be carried out using the product registered in the concerned Member State as the reference product

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

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.

In the case of oral solid forms for systemic action the test product should usually originate from a batch of at least 1/10 of production scale or 100 000 units, whichever is greater, unless otherwise justified. The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale; in case of production batch smaller than 100 000 units, a full production batch will be required. If the product is subjected to further scale-up this should be properly validated.

Samples of the product from full production batches should be compared with those of the test batch, and should show similar *in vitro* dissolution profiles when employing suitable dissolution test conditions (see Appendix II).

The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities.

In accordance with Annex 13 to the EU guide to GMP, reference and test product must be packed in an individual way for each subject included in the bioequivalence trial. Every effort should be made to allow a precise tracking of administration of the reference and test products to the subjects, for instance by the use of labels with a tear-off portion.

3.6 Data analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the reference and test products and to demonstrate that any clinically important difference is unlikely.

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 variable. A statistically significant sequence effect should be handled appropriately.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC, C_{max} should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation. The analysis technique for t_{max} should be non-parametric and should be applied to untransformed data. 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 Acceptance range for pharmacokinetic parameters

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 intervals for the main characteristics are detailed as follows:

<u>AUC-ratio</u>

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

In rare cases a wider acceptance range may be acceptable if it is based on sound clinical justification.

$\underline{C_{max}}$-ratio

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

In certain cases a wider interval may be acceptable. The interval must be prospectively defined e.g. 0.75-1.34 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations.

$\underline{t_{max}}$-diff

Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related 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_{min}, Fluctuation, $t_{1/2}$, etc.) considerations analogous to those for AUC, C_{max} or t_{max} apply, taking into consideration the use of log-transformed or untransformed data, respectively.

3.6.3 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 generally not 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.

3.6.4 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.

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. The results should be reported as profiles of percent of labelled amount dissolved versus time.

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 (see Appendix II).

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 principal investigator. The responsible investigator(s), if any,

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), finished product specifications and comparative dissolution profiles should be provided. In addition, the applicant should submit a signed statement confirming that the test product is the same as the one that is submitted for marketing authorisation.

All results should be clearly presented and should include data from subjects who eventually dropped-out. Drop-out and withdrawal of subjects 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 in 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 analysis to be repeated, e.g. randomisation scheme, demographic data, values of pharmacokinetic parameters for each subject, descriptive statistics for each formulation and period. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals including the method of their estimation ***sh***ould also be included.

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 suspension should be determined. In the case of a prodrug the intravenous reference solution should preferably be made of the active moiety.

4.2 Bioequivalence

During development bioequivalence studies are necessary as bridging studies between (i) pivotal and early clinical trial formulations; (ii) pivotal clinical trial formulations, especially those used in the dose finding studies, and the to-be-marketed medicinal product; (iii) other comparisons depending on the situation. Such studies may be exempted if the absence of differences in the in vivo performance can be justified by satisfactory in vitro data.

5 APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES

Bioequivalence studies

In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

The kind of studies to be performed may vary with the type of product, as follows.

5.1.1 Oral Immediate Release Forms with Systemic Action

This section pertains to dosage forms such as tablets, capsules and oral suspensions and takes into consideration criteria derived from the concepts underlying the Biopharmaceutics Classification System, i.e. high solubility, high permeability for the active substance and high dissolution rate for the medicinal product. These criteria, along with a non-critical therapeutic range should be primarily considered; therefore the following characteristics have to be taken into account in order to justify the request for exemption from in vivo bioequivalence studies.

a) Characteristics related to the active substance:

i - risk of therapeutic failure or adverse drug reactions:

this risk depends on the requirements of special precautions with respect to precision and accuracy of dosing of the active substance, e.g. the need for critical plasma concentrations;

ii - risk of bioinequivalence,

evidence of bioavailability problems or bioinequivalence exists for some specific active substances;

iii – solubility:

This parameter is a major criterion to justify exemption from in vivo studies. When the active substance is highly water soluble, the product could be in general exempted from bioquivalence studies unless, considering the other characteristics, the exemption could entail a potential risk. Polymorphism and particle size are major determinants of dissolution rate and special attention should be paid to these characteristics. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 ml of each of three pharmacopoeial buffers within the range of pH 1-8 at 37ºC (preferably at or about pH 1.0, 4.6, 6.8);

iv - pharmacokinetic properties

linear and complete absorption reduces the possibility of an immediate release dosage form to influence the bioavailability.

b) Characteristics related to the medicinal product:

i - rapid dissolution

in case of exemption from bioequivalence studies, in vitro data should demonstrate the similarity of dissolution profile between the test product and the reference product. However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution profiles may be accepted as demonstrated (see appendix II);

ii – excipients

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 of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted;

iii – manufacture

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 pharmaceutics section of the dossier.

5.1.2 Oral solutions

If the product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance.

In those cases where an oral solution has to be tested against an oral immediate release formulation 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 and transdermal dosage forms

Requirements for bioequivalence studies in accordance with the specific guideline

5.1.5 Fixed combinations products

Combination products should in general be assessed with respect to bioavailability and bioequivalence of individual active substances either separately (in the case of a new combination) or as an existing combination. Criteria under 5.1.1 will apply to individual components. The study should be designed in such a way that the possibility of a pharmacokinetic drug-drug interaction could be detected.

5.1.6 Parenteral solutions

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

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required.

5.1.7 Gases

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

5.1.8 Locally applied products

a) Locally acting

For products for local use (after oral, nasal, inhalation, 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. The lack of them should be justified (see specific Note for Guidance).

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

b) Systemically acting

For locally applied products with systemic action a bioequivalence study is always required.

5.1. In Vitro Dissolution

Dissolution studies are always necessary and consequently required. In some cases those studies are alone sufficient to assess the bioequivalence but in other cases they are insufficient and should be completed by in vivo studies. Dissolution studies must follow the guidance as laid out in Appendix II.

5.2. Variations

If a product has been reformulated from the formulation initially 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 product undergoing change has been investigated and an acceptable correlation between in vivo performance and in vitro dissolution has been established, the requirements for in vivo demonstration of 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 (see Appendix II)

In all other cases bioequivalence studies have to be performed.

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

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

5.3. Dose proportionality in immediate release oral dosage forms

If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. Furthermore all of the following conditions should be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process;
- the drug input has shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used);
- the qualitative composition of the different strengths is the same;
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance, the ratio between the amounts of 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 (within the approved dose range) 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.

5.4. Suprabioavailability

If suprabioavailability is found, i.e. if the new product displays an extent of absorption appreciably larger than the approved product, reformulation to a lower dosage strength should be considered. In this case, 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 suprabiovailable product will have to be supported by clinical studies if different from the reference product. Such a pharmaceutical product should not be accepted as therapeutically equivalent to the existing reference product. If marketing authorisation is obtained, the new product may be considered as a new medicinal product.

To avoid confusion for both prescribers and patients, it is recommended that the name of 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

Explanation of the symbols in paragraph 3.3

C_{max}: maximal plasma concentration;

C_{min}: minimal plasma concentration;

C_{av}: average plasma concentration;

t_{max}: time passed since administration at which the plasma concentration maximum occurs;

AUC_t: area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_∞: area under the plasma concentration curve extrapolated to infinite time;

AUC_τ: AUC during a dosage interval in steady state;

MRT: mean residence time;

Ae_t: cumulative urinary excretion from administration until time t;

Ae_∞: cumulative urinary excretion extrapolated to infinite time;

$t_{1/2}$: plasma concentration half-life;

Fluctuation: $(C_{max} - C_{min})/C_{av}$ or $(C_{max} - C_{min})/C_{min}$

APPENDIX II

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:

i - Quality assurance

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for 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

ii -Bioequivalence surrogate inference

- To demonstrate similarity between reference products from different Member States
- To demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product
- To collect information on batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in vivo study.

The test methodology should be in accordance with pharmacopoeial requirements unless those requirements are 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 an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, 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 case history 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 are insensitive to pH, profiles from only two buffer systems are required.

If an active substance is considered to have a low solubility and a high permeability, the rate

limiting step for absorption may be dosage form dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the active substance. In those cases a variety of test conditions is recommended and adequate sampling 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.

Any methods to prove similarity of dissolution profiles are accepted as long as they are justified.

The similarity 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:

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

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 (zero excluded)
- 12 individual values for every time point for each formulation
- not more than one mean value of > 85% dissolved for each formulation
- that the standard deviation of the mean of any product 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.