Bioequivalence assessment and the conduct of bioequivalence trials: a European point of view

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INTRODUCTION

Generic drugs have been introduced on the pharmaceutical market, mainly to reduce drug expenses by the consumers and health care authorities. In the European Union, generic drugs can be approved using an ‘abbreviated procedure’. Indeed, it is not necessary for a generic drug to introduce a complete report, because such a dossier has been approved in the past for the innovator drug. The submission needs to contain only a bibliographic file of the properties of the drug, a complete pharmaceutical dossier attesting the analytical qualities of the generic drug, and a study establishing bioequivalence between the generic drug and the innovator product. Bioequivalence assessment of generic drugs with innovator molecules is required in order to exclude any clinically significant difference in the rate and extent to which the active moiety becomes available at the site of drug action and hence to protect the consumer from any difference in activity of the generic as compared to the innovator.

In 1991, the Commission of the European Communities (EC) released a note for guidance for the ‘Investigation of bioavailability and bioequivalence’ (1). Although being rather complete, the guideline does not cover special situations that may raise problems or at least questions in bioequivalence trials. In addition, the guideline does not specify all practical aspects that have to be considered when planning and carrying out such a trial. In fact, in writing the guideline, it was the willingness of the authors not to be excessively precise and to remain open to other approaches or procedures that appear scientifically sound and make the consensus in the scientific community.

Therefore, the clinical investigator has some margins of manoeuvre and must use scientific and clinical common sense to carry out its investigation.

In this paper, we would like to discuss some aspects of bioequivalence testing, with the hope that it may help to find solutions to unanswered questions until the necessity and possibility is considered to amend the guideline.

BIOAVAILABILITY AND BIOEQUIVALENCE

The European guideline specifies that ‘the bioavailability of an active substance from a pharmaceutical product should be known and reproducible. This is especially the case if one product is substituted for another. In that case, the product should show the same therapeutic effect in the clinical situation’.

By bioavailability, the Commission of the European Community (EC) ‘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’. It is specified that for drugs intended to exhibit a systemic therapeutic effect, bioavailability can be more simply understood as ‘the rate to which a substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation’. Indeed, in the case of such drugs, ‘the substance in the general circulation is in exchange with the substance at the site of action’.

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Thus, for a generic drug, the EC requires therapeutic equivalence with the innovator molecule. However, in view of the difficulties in establishing therapeutic bioequivalence, ‘pharmacokinetic data instead of therapeutic results may be used to establish equivalence: bioequivalence’.

Thus ‘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’.

The difference between pharmaceutical equivalent and alternative is that the former is a medicinal product containing the same amount of the same active substance(s) in the same dosage form, while the latter contains the same therapeutic moiety but differs in chemical form (salt) or in the dosage. Thus, the EC may accept therapeutic equivalence not solely between pharmaceutical equivalents but also between alternatives.

The EC is also using the term ‘essentially similar product’ that applies to a proprietary medicinal product that has the same qualitative and quantitative composition in terms of active principles as the innovator, is presented in the same pharmaceutical form, and, where necessary, is bioequivalent with the innovator product.

**WHEN IS BIOEQUIVALENCE REQUIRED?**

The guideline specifies, in 2 separate sections, the situations in which a bioequivalence study is required and those in which bioequivalence is not required, respectively. In fact, for products intended to be delivered into the general circulation, a bioequivalence study is always required, except in the following situations:

(a) the product differs only in strength of the active substance provided that pharmacokinetics are linear and the composition of the product is the same and produced by the same manufacturer at the same production site.

(b) the product is a liquid oral form, a parenteral solution or a gas for inhalation identical (active substance and excipients) to approved medicinal product.

(c) the product is for local use (after oral, nasal, ocular, dermal, vaginal application...) and intended to act without systemic absorption.

Concerning parenteral solutions, the situation is rather clear for drugs to be administered intravenously. But, is a bioequivalence study required for drugs to be given intramuscularly (i.m.) or subcutaneously (s.c.). According to section 5.2 (Exemptions) of the guideline, the answer is no. However, according to section 5.1 the answer is yes. Indeed in this section, it is indicated that a bioequivalence study is required for ‘non-oral immediate release products’. Therefore, it would appear reasonable to provide a bioequivalence study for i.m. and s.c. administered drugs.

For products for local use, safety and pharmacodynamic or clinical studies are required to establish therapeutic equivalence.

**DESIGN OF A BIOEQUIVALENCE STUDY**

The preferred approach is an in vivo study carried out in healthy volunteers or patients to whom the 2 preparations (generic and innovator) are alternatively administered. The study should be designed in such a way as to distinguish treatment from other effects. In this respect, a cross-over design is the first choice with a random allocation of the subjects to the treatment sequences.

For most of the cases, a single-dose study is adequate. However, repeated-dose studies with measurements at the steady-state may be required in addition to the single-dose study, for instance for sustained-release products or for drugs with highly variable pharmacokinetics or dose- or time-dependent pharmacokinetics. Of course, the study should conform to EC rules for Good Clinical Practice, should be approved by an ethical committee, and the volunteers must give their informed consent in writing. The study should also be covered by an adequate insurance.

**The reference formulation**

The reference formulation is the innovator product marketed in the country where the submission is made. Problems may arise when a bioequivalence study has been carried out in one European country and a submission is made in an other European country where the innovator is marketed in a slightly different form (e.g. difference in excipients). In this case, and if applicable, the applicant should try to convince the regulatory authorities that the difference is totally irrelevant for the bioavailability of the product. If this cannot be done but appears probable,