Amended guideline of the European Medicines Agency on the investigation of bioequivalence

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Introduction

Generic medicines, being equivalents of original medicinal formulations, constitute nearly half of all pharmaceutical preparations used today in Europe. It is estimated that they are by about 20÷90% less expensive than the original products [1], the reason for this being the simplified marketing procedure: drugs registered as generics do not require the full scope of pre-clinical studies and clinical trials. However, to be able to market a generic, it must be proved that the active ingredients, strength and pharmaceutical form are identical (or equivalent) with the innovator product, and that the quality, efficacy and safety of the generic drug is similar to that of the original, which must be confirmed by appropriate tests.

Both the 2001/83/EC Directive [2], as well as the Polish Pharmaceutical Law [3], requires that the therapeutic equivalence of a generic and the reference drug be demonstrated by appropriate studies of bioequivalence performed on humans. The notion of bioequivalence is of fundamental importance to generic medicines.

Studies of equivalence enable establishing the clinical significance of technological variations between batches of the drug at different levels of technological development, as well as justification of interchangeability of medicinal products in clinical practice. For this reason the issue is crucial for both the pharmaceutical industry, as well as for healthcare institutions and insurance companies.

New recommendations

An amended guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) became effective on the 1st of August last year [4]. It replaced a former one, which was formulated in 1998 and became effective in 2002 (CPMP/EWP/QWP/1401/98 – Note for guidance on the investigation of bioavailability and bioequivalence) [5] and the document related to it: CHMP/EWP/40326/06 (Question and Answers on Bioavailability and Bioequivalence Guideline) – Q&A [6]. The guideline, which from the legal point of view is a set of recommendations of the Committee for Medicinal Products for Human Use (CHMP) , a scientific advisory committee of the European Medicines Agency (EMA), owes its current form to the initiative of CHMP's work group on pharmacokinetics, which in 2007 started a discussion on the need to revise the guideline.

The approval of the amended guideline by CHMP in January 2010, followed by its entry into force, was by no doubt a significant event for the pharmaceutical industry (first of all the generics industry), as well as for the people and institutions engaged in the work on the investigation of bioequivalence. These circles have for a long time discussed the need to modify the legislation pertaining to the design and execution of bioequivalence studies. The need to make the wording of the guideline more precise, to supplement it or even to change it, was voiced many a time. The response was the publication by CHMP in 2006 of a document referring to the most frequently raised issues. That document was in the form of questions and answers [6]. Despite that, the European recommendations still remained insufficiently detailed and impractical, as compared to, for instance, American FDA recommendations.

The new guideline is formally consistent, is clearly and logically structured, and comprises more unambiguous provisions than its predecessor. It deals with many specific problems associated with bioequivalence studies. Its individual sections refer to all issues raised in the Q&A document [6].

Area of impact

The amendment of the guideline also changed the scope and area of its impact. While the former version included definitions, goals and methods of studies on bioavailability, and its specific component – bioequivalence studies, the new one pertains exclusively to the bioequivalence studies of medicinal products. This contracts the area of its impact, by excluding the study of drug fate in the organism, performed at different levels of drug development (such as the study of the level of availability of new substances, differences in absorption of various forms and doses of the same drug, etc.), but on the other hand it enables more precise formulation of recommendations specific for bioequivalence.

In addition, the provisions of the guideline itself confine its applicability even in many cases of bioequivalence studies. The guideline states that its recommendations apply to formulations with systemic action, with classical (immediate) release of active ingredients, and are restricted to drugs containing a chemical entity as the active ingredient, and in principle they do not apply to herbal medicines and are limited to the presentation of requirements for studies based on pharmacokinetic endpoints. This in principle excludes from the direct impact of the recommendations of the guideline a major group of modern medicinal products in which the pharmaceutical companies' interest is growing. These include modified release preparations, biological drugs, herbal and natural preparations. The guideline does also not include provisions specifically related to complex formulations.

The objective of the guideline, as stated in its introduction, is the presentation of EMA requirements for the design, conduct and evaluation of bioequivalence studies of drugs and the definition of conditions of replacing them with *in vitro* studies.

Major changes

The most significant changes in the amended guideline pertain to the model of studies (introduction of the so-called two-stage design, among others), justification of the selection of the substance determined (metabolites, enantiomers), criteria of statistical acceptance of bioequivalence and conditions for exempting *in vivo* studies (biowaivers, bracketing approach).

The guideline, while in principle focussing on studies performed with the aim to register generic products, pursues to address most of the problems that have for a long time been identified in bioequivalence studies [7]. In fact, in comparison to the previous version, much more stress has been laid on the detailed description of the manner of carrying out studies of endogenous substances, enantiomers, highly variable drugs and narrow therapeutic index products. The issue of using urine as the biological matter is also dealt with in more detail.

Study design

The amended guideline complements the provisions of the previous one. The principles remain unchanged. The single-dose crossover design is still the standard design. At the same time conditions for

applying alternative designs are defined: study on parallel treatment groups, replicate study design, or multiple dose study, the conduct of which is restricted by the new guideline to specific cases, e.g. when administration to volunteers is not acceptable due to the toxicity of the active ingredient, while providing a single dose to a patient is unethical.

The least number of changes has been made to the section on subjects and standardization of studies. Studies should be conducted on a group of healthy volunteers that can belong to either sex and be subjected to geno- or phenotyping. As in the previous version, the adopted minimum number of subjects is 12. This is a theoretical value, as a rule not applied in studies conducted for registration purposes. The sense of this provision is more apparent in relation to the possibility of applying the two-stage design. In this context the number of subjects in the first stage should not be less than 12.

The guideline describes in detail the manner of selecting the reference product; the significance of *in vitro* release tests (pharmaceutical equivalence) for the proper selection of the reference product batch and for the preparation of the product studied for bioequivalence assessment is highlighted. Information on the conditions of approving test products for the studies, which was also given in the previous version, is now arranged in a more orderly manner.

The application of the study under fed conditions is basically restricted to situations when this is the only recommended manner of reference drug intake. In the case of some forms of drug (microemulsions, solid dispersions) the guideline recommends performing the studies under both fasted and fed conditions. In studies performed under fed conditions the manner of administering the product with the meal is described in detail along with the composition of the standard meal during the investigation of the impact of the meal.

As an independent document on bioanalytical methods is currently under development [8], the problem of analysis of the compound studied has been limited to the necessary minimum. Lack of acceptance of sample analysis repeated for pharmacokinetical reasons is confirmed and the inadmissibility of such procedure without previously taking account of it in the study report is stated. It is also stated that material analysis should be performed while observing the rules of concealing the identity of the studied products (triple blind trials). The guidelines for the frequency of blood sampling for pharmacokinetic studies are essentially retained. Attention is drawn to sampling times in order to avoid obtaining maximum concentration in the first sample taken. In addition, the amended guideline introduces the possibility of terminating sampling after 72 hours in the case of drugs of long half life (determination of $AUC_{0\text{-}72h}$ instead of AUC_t).

The issue of substances determined in the study is accounted for very extensively. CHMP experts recognize the concentration of the parent compound as the most reliable parameter for detecting the differences between products (parent compound defined as metabolically unchanged substance introduced into the organism in the given form of drug). The new guideline indicates that with the now available, sensitive and precise analytical methods, bioequivalence evaluation should be based upon measured concentrations of an unchanged substance. This principle also applies to prodrugs. Only in exceptional situations (low concentration of unchanged drug in blood, quick elimination of unchanged substance) does the guideline allow the determination of the main pharmacologically active metabolite upon very detailed justification and proof of an objective lack of choice of other procedure.

The issue of conditions for abstaining from bioequivalence study of different strengths of the same product are presented in great detail in the amended guideline. A novel term and recommendation of the so-called bracketing approach is introduced. In this case study is performed for the extreme strengths only.

The exempting of *in vivo* studies based on BCS classification and positive results of extended *in vitro* studies is another issue thoroughly discussed in the new version of the guideline, as is the issue of the methodology of *in vitro* dissolution studies to complement or replace equivalence studies. In addition to sections of the main body of the guideline, there are also ample appendices devoted to these topics.

Statistical evaluation of results

The vague approach to statistical evaluation of study results in the previous version is now dealt with more precisely. Basic parameters determining bioequivalence are clearly defined. These include: AUC_t (or $AUC_{0\text{-}72h}$) and C_{max} – for studies after single dose administration, and $AUC_{0\text{-}\tau}$ and $C_{max,\ ss}$ – for steady state studies, or $Ae_{0\text{-}t}$ and R_{max} – for studies using urinary data. Statistical evaluation of t_{max} is not required for the assessment of bioequivalence.

Acceptance criteria for basic pharmacokinetic parameters are defined more precisely. According to the new guideline, the acceptance interval for the 90% confidence interval of the ratio of the test and reference drugs, for both AUC and C_{max}, must in general be contained between 80.00 and 125.00%. The acceptance interval may be widened for C_{max} only in the case of highly variable drug products, for which a wider difference in maximum concentration has no clinical significance (the acceptance interval may be widened to: 69.84÷144.19%). For drugs with a narrow therapeutic index, tighter acceptance criteria are recommended (90.00÷111.11%).

More attention, in comparison with the previous version, is paid to presenting the criteria for rejecting results during statistical analysis.

Undoubtedly, one of the most spectacular novelties that has a fundamental impact on the practice of conducting equivalence studies is the possibility of terminating the study after completing the first stage thereof and establishing the existence of or the lack of bioequivalence (two-stage design). It is possible to calculate the final number of volunteers based on the variability of pharmacokinetic parameters determined in the first stage of the study. This enables completing the study with a negative result using fewer participants than in the case of traditional approach or reducing the number of volunteers by precisely estimating it during the experiment.

Additionally a number of formal provisions were introduced in the new guideline. The most important seem to be: the requirement to perform the study in accordance with the principles of the Good Clinical Practice defined by Directive 2001/20/EC, the requirement to manufacture and package the products studied in accordance with GMP, in individual pieces of packaging, separately for each subject and period. An encouragement was also formulated for the manufacturers to contact CHMP for scientific advice for the design of studies.

Summary

To recapitulate, the major value of the modified requirements presented by CHMP is the orderly arrangement of notions and unambiguous presentation of a standard form of bioequivalence study. This 'gold standard' is as follows: crossover study upon administration of one dose under fasting conditions, conducted on a group of healthy volunteers, with basic parameters, AUC and C_{max}, determined from concentrations of unchanged substances in blood. All other designs of study, according to the guideline, are applicable in specific cases only. The problem, however, is that in view of the growing intensity of drug trials and of increasingly sophisticated manufacturing methods; the number of specific cases is exceptionally high.

The narrowing of the area encompassed by the new guideline, justified by the more detailed approach to the major issues, translates into an evidently stiffened EMA's position in relation to possible modifications to the methodology of equivalence studies performed for registration purposes. The guideline provisions do not allow taking an individual approach to handling problems encountered in a specific

project. The guideline includes a provision enabling the application for approval of a non-standard approach in a specific case, but this is only a theoretical possibility. Anyone who came across European registration procedures understands that very well.

The phrase, which occurs in the guideline many times and convinces that it is possible to determine virtually any compound, in any amount, with analytical confidence, confirms the Agency and its experts in the conviction that the standard procedure is applicable in every situation. It frequently also happens that methodological requirements and assessment criteria, that follow the spirit and letter of the guideline, are applied directly also to drugs that in theory are not subject to its provisions, e.g. to modified release products, or to biopharmaceuticals.

The study of bioequivalence is a specific one. It is not deemed directly equivalent to clinical trial, as its main objective is not the discovery of new properties of a medicinal substance, but the demonstration of the lack of difference between the medicinal products studied, and in fact between the various manufacturing methods. The crossover study design, careful standardization of study conditions and methods, along with tight acceptance criteria, serve this purpose, and approximate, in terms of methodology, the equivalence studies to qualitative analytical methods. The clinical results, however, cannot be standardized in a manner similar to pharmacopeial methods. Therefore it is hard to expect that even such an up-to-date and precise guideline, as the one released by CHMP last year, will encompass all cases that can occur in real life. It is certainly a step in the right direction, one that was expected and generally well accepted. It seems, however, that it is time to proceed further and develop detailed indications for specific drugs. Perhaps it would be a good idea to draw on the experience of FDA, which, since 2007, has been publishing short, although sufficient, recommendations on the design of studies of individual active compounds of defined pharmaceutical form, the so-called Individual Product Bioequivalence Recommendations. Time will show if the European institutions will be willing to follow the same path.

Literature

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