

Editorial

**BIOEQUIVALENCE,
THERAPEUTIC EQUIVALENCE
AND GENERIC DRUGS**R.K. Verbeeck

Between 1995 and 2002 I served as an external expert to the Belgian Medicines Evaluation Board and during those 8 years I assessed most, if not all, dossiers in which one or more bioequivalence studies were described as part of the application for marketing authorization of a medicinal product. During that period I evaluated more than 400 bioequivalence studies submitted for marketing authorization of generic drug products in Belgium via the National Procedure or via the Mutual Recognition Procedure of the EMEA (European Medicines Agency). I therefore read with much interest the articles on generic drugs by Dupont and Heller and Heller and Dupont which appear in this issue of *Acta Clinica Belgica* (1,2).

Clinical experts generally agree that a bioequivalence study is the most appropriate approach for demonstrating therapeutic equivalence between two drug products and the value of bioequivalence as a surrogate for therapeutic equivalence is not questioned (3,4). Consequently, bioequivalence studies have been for many years an essential part of registration dossiers not only for generic drug products but also for innovator drug products (4,5). For example, registration of the majority of orally administered innovator drug products is based on one or more bioequivalence studies for the simple reason that in most cases the formulation that will be marketed is not the same as the formulation that was used in the clinical efficacy/safety studies during the clinical phases of drug development (5). A bioequivalence study, a so-called "bridging study", is in those cases necessary to demonstra-

te therapeutic equivalence between the "clinical" and the final "market image" formulation of the innovator drug product. Thus for the majority of new drugs administered orally, clinical studies were not carried out on the final "market image" formulation, just as is the case for generic drugs.

Although the general principle that bioequivalence is a surrogate marker of therapeutic equivalence is not questioned, the discussion regarding the therapeutic equivalence between generic drugs and innovator drugs continues unabatedly. The pharmaceutical companies see their sometimes huge profits plummet as soon as the patent protection on their drug products expires and the market is taken over by much cheaper, but therapeutically equivalent, generic drugs. From a pure marketing standpoint, discrediting the principle that generic drugs are therapeutically equivalent to their innovator counterparts, therefore, may seem to be an effective approach to try to ensure that these high profits continue even after patent protection has expired. Health professionals, however, should be objectively and correctly informed about the quality and therapeutic equivalence of generic drugs and their prescription behaviour should be guided by a correct understanding of the real important issues regarding the use of generic drugs.

In their articles, Dupont and Heller do not really provide a clear explanation and balanced view of the important issues regarding bioequivalence and therapeutic equivalence (1,2). Both articles are a collection of incompletely explained principles and (mostly) anecdotal reports regarding bioequivalence assessment and the notion of therapeutic equivalence. Indeed, although the authors recognize that "*there are very few well-conducted prospective studies that enable one to analyse whether generics meet pharmaceutical and clinical quality criteria*", they nevertheless continue to

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the rate of absorption of the active substance following oral administration of the two formulations may be different, which is not really the case. The primary metrics used to assess bioequivalence are AUC_t (the area under the plasma concentration-time profile of the active substance), C_{max} (the maximum plasma concentration of the active substance) and t_{max} (the time at which C_{max} is reached). AUC_t is the bioequivalence metric describing the extent of absorption, t_{max} is the metric which characterizes the rate of absorption, and C_{max} is influenced by both extent and rate of absorption (4,10). To demonstrate bioequivalence between two oral formulations the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence recommends to calculate the 90% confidence interval around the geometric mean ratios of both AUC_t and C_{max} for Test (generic) and Reference (innovator) (12). These 90% confidence intervals should, in most cases, be located within the 0.80 – 1.25 acceptance limits. (To fully understand why this particular statistical test is used in bioequivalence assessment and how to interpret the results, the interested reader should consult one of several excellent books recently written on this subject (e.g. 4,10)). A statistical evaluation of t_{max} , the metric characterizing rate of absorption, is indeed not generally required according to the EMEA guidelines: "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" (11). I would like to make the following brief remarks regarding Dupont and Heller's statement (see above) on rate of absorption. First, the EMEA Note for Guidance clearly states that the confidence interval for t_{max} should lie within a clinically determined range if there is a clinically relevant claim for rapid release or action or signs related to adverse effects. This means that for medicinal products which act acutely - e.g. hypnotics, hypoglycemics, analgesics for acute pain - rate of absorption is a critical factor as far as activity and safety is concerned and, therefore, t_{max} has to be similar between two medicinal products in order to be bioequivalent. Second, although C_{max} is affected by both rate and extent of absorption, in the context of bioequivalence studies C_{max} is often referred to as the metric characterizing rate of absorption. Indeed, when two plasma concentration-time profiles show bioequivalence for both AUC_t and C_{max} , not only the extent of absorption but also the rate of absorption between the two medicinal products will normally be very similar.

Although C_{max} is the standard regulatory measure of rate of absorption, it should be mentioned that it has several drawbacks (4). Therefore, in the revised EMEA bioequivalence guidelines the partial AUC, truncated at the population median of t_{max} for the reference formulation, is recommended as a measure of early exposure for products where rapid absorption is of importance (12). Third, most drugs are administered as a multiple dose regimen and efficacy and safety depend on steady state plasma concentrations of the active substance. Unlike extent of absorption, rate of absorption is in most cases not a critical determinant of drug efficacy and safety under steady state conditions, especially considering the fact that C_{max} values have to be in all cases very similar between two bioequivalent medicinal products. It is in this context that the recommendations of authorities such as the FDA (US Food and Drug Administration) and EMEA concerning bioequivalence assessment should be interpreted. But it is also clear from my brief comments that the principles underlying the methods for bioequivalence assessment are not simple and, it is fair to say, not well known to most health professionals.

On the issue of therapeutic equivalence between oral medicinal products containing active substances with a narrow therapeutic index, the major authorities issuing bioequivalence guidelines do not share the same opinion. On the one hand, the FDA does not recommend stricter norms for narrow therapeutic index drugs (13). Their standpoint is very clear: "FDA recognizes the scientific concept that drugs differ in their therapeutic range. However, because of FDA's strict bioequivalence criteria, we believe that drugs do not fall into discrete groups that would allow one to consider NTI (Narrow Therapeutic Index) drugs as being clearly different from other drugs for purposes of therapeutic substitution" (13). This means that for narrow therapeutic index drugs to be bioequivalent the FDA guidelines require the 90% confidence interval around the geometric mean ratio of C_{max} and AUC_t to be located within the usual acceptance range of 0.80 to 1.25. For narrow therapeutic index drugs, the Health Product and Food Branch (Health Canada) and the EMEA, on the contrary, recommend to apply stricter bioequivalence criteria. In 2006 Health Canada, published a short document entitled "Bioequivalence Requirements: Critical Dose Drugs" (14). In this document a list of 9 drugs is given, i.e. cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus and theophylline, for which Health Canada recommends that the 90% confidence interval for AUC_t be located within the 0.90 to

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