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Commentary

Theme: Pharmacokinetics, Biopharmaceutics and Bioequivalence: History and Perspectives
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The Two Main Goals of Bioequivalence Studies

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Abstract. The principal goal of bioequivalence (BE) investigations has crucial importance and has been the subject of extensive discussions. BE studies are frequently considered to serve as procedures for sensitive discrimination. The BE investigation should be able to provide methods and conditions sensitively identifying relevant differences between drug products if such differences in fact exist. Alternatively, BE studies can be deemed as surrogates of clinical investigations assessing therapeutic equivalence. Bioequivalent drug products will be provided to patients for their benefits. Both points of view are valid since they represent two aspects of product performance. It has been argued that both should be equally sustained and applied. In practice, however, they collide when regulatory conditions and statements are developed. For instance, some regulators prefer to conduct BE studies following single drug administrations since these conditions are considered to provide the highest sensitivity of discrimination between pharmacokinetic profiles and thus, a product's *in-vivo* performance. Others suggest that, at least for modified-release products, BE investigations should be performed in the steady state since it represents clinical conditions. Preference for one point of view or the other pervades other regulatory statements including suggestions for subjects to be selected in studies and pharmacokinetic measures to be evaluated. An overview is provided on the disturbing inconsistency of statements within and between regulations. It is argued that harmonization would be highly desirable, and relevant recommendations are offered.

KEY WORDS: bioequivalence; clinical surrogate; product performance; regulatory expectations; sensitive discrimination.

INTRODUCTION

It is always important to establish and recognize the goal(s) of an investigation before it is undertaken and evaluated. This is true also about studies of bioequivalence (BE). The issue is not trivial and not straightforward and has been the subject of extensive discussions during previous decades (1–6).

BE studies evaluate and compare pharmacokinetic (PK) parameters of two (or more) drug products. The investigations are frequently considered to serve as procedures intended to confirm comparable biopharmaceutical properties between pharmaceutical equivalents (same active ingredient, same dose, same/comparable dosage form). A generic product being evaluated in order to gain marketing authorization should satisfy clear and stringent regulatory acceptance criteria in comparison with a reference product being approved which is based on full clinical documentation. In order to achieve this goal, a BE investigation should be performed under conditions, and analyzed in a way, which are able to identify the most sensitive method for identifying the presence of relevant differences in the rate and extent of exposure across the investigated drug products should such differences in fact exist. Thereby, the conditions and analyses will provide most sensitive discrimination between the PK parameters of the investigated formulations.

Alternatively, BE studies can be viewed as therapeutic surrogates for confirming product therapeutic equivalence in clinical investigations. The drug products will be provided for the benefit of patients. Therefore, bioequivalent formulations should yield closely similar clinical profiles in subjects, *i.e.*, they should exhibit therapeutic equivalence. Thus, it has been argued that BE investigations should be pursued and assessed under clinically relevant conditions (3).

In this context, it should be taken into consideration that this paradigm does not necessarily work the other way round.

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There are cases where therapeutic equivalence might be demonstrated (by means of clinical studies assessing therapeutic efficacy) for certain medicinal products even though bioequivalence in terms of pharmacokinetic assessments cannot be confirmed for these preparations. Receptor blocking agents (*e.g.*, beta-receptor antagonists) may serve as a very conclusive example in this respect. Up to a certain dose level, an exposure-effect relationship may be shown, but clinical effects will not further increase with rising doses or exposure if (almost) all receptors are already occupied. Consequently, bioequivalence may be considered indicative for therapeutic equivalence but not necessarily *vice versa*.

Both views of BE studies, to ensure sensitive discrimination between PK parameters and to provide therapeutic equivalence, are valid. They are two aspects for obtaining and maintaining comparable product performance. It has been argued that both views should be sustained and applied (2). In practice, however, they can collide when regulatory conditions and statements are developed. This can lead to inconsistencies and uncertainties.

This commentary will discuss differing consequences of the two viewpoints. Respective study conditions and measures of evaluation will be noted. They will be illustrated on some of the regulatory expectations of the US Food and Drug Administration (FDA) (7,8) and also of the European Medicines Agency (EMA) (9) and Health Canada (10). In this context, it should be noted that these considerations are only focused on systemic drugs for which systemic exposure is an essential condition for exhibiting clinical efficacy (and/or safety). Non-systemic ("topical") drugs will not be discussed in the following as the conventional bioequivalence concept is not applicable for these cases.

The commentary is intended to serve as a platform for stimulating discussion on these issues. We hope that the exchange of views and suggestions will help to resolve the discrepancies. We shall host a discussion of this paper on the AAPS blog. We invite readers' responses and thoughts on concerns raised in this communication and any recommendations they may wish to proffer.

CONDITIONS FEATURING THE TWO MAIN GOALS OF BIOEQUIVALENCE STUDIES

The regulatory authorities recommend several conditions and metrics which they judge to be favorable for the determination of bioequivalence. Their judgment tends to prefer one or the other of the main goals, either that of sensitive discrimination or therapeutic surrogate.

Some of the conditions and metrics are presented in Table I. The conditions include the suggested study population, either that of healthy volunteers or a sample representative of the general population. Healthy volunteers, especially just young males, would be sufficiently homogenous to enable sensitive discrimination between the investigated drug products. In contrast, a representative sample is comparatively heterogeneous but reflects more the population which is expected to receive the drug.

The recommendations to undertake single-dose rather than multiple-dose studies, and to apply data, whenever possible, from the parent drug instead of its active metabolite, reflect the importance of sensitive discrimination. Moreover, the parent drug should characterize performance more directly than the metabolite as its formation additionally includes biochemical processes. In contrast, the suggestion, that the metric C_{max} rather than C_{max}/AUC should be evaluated, corresponds to the clinical view. Each of these conditions and metrics will be discussed in greater detail below.

Two inconsistencies can be gleaned from Table I:

- First, there are both similarities and differences in the study conditions recommended across the various regulatory authorities. For example, the US-FDA and Health Canada recommend single-dose studies both for immediate and extended/prolonged-release products, whereas EMA (as in the past also Health Canada) requests also steady-state investigations for those extended/prolonged-release formulations which have the potential of accumulation.
- Second, the regulatory agencies appear to be internally inconsistent when stating their preference either for sensitive discrimination or clinical representation. For instance, FDA states explicitly and emphatically that the pursuit of single-dose studies and analysis of the parent drug is expected because they yield more sensitive discrimination between the investigated preparations. At the same time, FDA expects the analysis of C_{max} and a study sample which is representative of the underlying population thereby reflecting a more clinical view.

The sensitivity of discrimination is affected by the variability of the drug products. For instance, the magnitude of the within-subject variation is one of the principal factors determining how close the calculated confidence limits would be to the preset BE limits. Regulatory authorities are not always harmonized on the relation between variation and BE

Table I. Conditions and Metrics Recommended by Regulatory Authorities

Condition or metric	Sensitive discrimination	Therapeutic surrogate
Study population	(Young) healthy (male) volunteers[a,b]	Heterogeneous, representative sample[c]
Single/multiple dosing	Single dosing[a,c]	Multiple dosing (for accumulating ER/PR formulations)[b]
Parent drug/metabolite	Parent drug[a,c,b]	Active metabolite
Metric for absorption rate	C_{max}/AUC	C_{max}[a,c,b]

[a] Recommended by Health Canada
[b] Recommended by EMA
[c] Recommended by FDA

limits. For example, the BE limits set by EMA (and also Health Canada) differ from those recommended by FDA for the determination of BE of highly variable drugs (11,12).

Choice of Subjects: Discriminatory or Representative Sample?

Various regulatory authorities place differing emphases on choosing subjects for undertaking BE studies. Some stress the importance of sensitive discrimination between the test and reference drug products. The guideline of EMA suggests (9): "The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical."

Similarly, the guideline of Health Canada recommends (10): "To minimize variability, comparative bioavailability studies are usually conducted with normal, healthy volunteers (male and/or female)."

The 2014 FDA draft guidance on new drug applications (NDAs) and those for investigational new drugs (INDs) also suggests (8): "In general, BA and BE studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is likely to produce less PK variability compared with that in patients."

On the other hand, the 2013 draft guidance of FDA on abbreviated new drug applications (ANDA) states (7): "*In vivo* BE study subjects should be representative of the general population, taking into account age, sex, and race. If a drug product is intended for use in both sexes, the applicant should include similar proportions males and females in the study."

The expectations of regulatory agencies for choosing a sample for a BE study are important. The evaluation of crossover BE investigations are based on within-subject variations. On the other hand, regulatory guidelines referring to the choice of subjects involve between-subject variations. However, the between- and within-subject variation of area under the curve (AUC) is highly correlated (13). Therefore, statements of the regulators are relevant in this regard. Altogether, EMA and Health Canada call for discriminatory sensitivity. So does the FDA draft guidance for NDAs and INDs. However, the FDA draft guidance for ANDAs emphasizes the need for a sample of subjects representative of the general population, a view which is closer to that of a BE study being a surrogate of a clinical investigation.

Arguments can be offered in favor of both discriminatory sensitivity and clinical relevance for the selection of subjects in BE studies. More widely, clinically representative samples could reveal potential subject-by-formulation interactions. However, it could be very difficult to detect and identify such interactions with the usual sample sizes of BE investigations particularly since variations would probably be larger in a more general population. This could be a reason for the regulatory suggestion that BE studies be undertaken in healthy volunteers unless this is hazardous and unethical.

For some special populations, for instance pediatric, geriatric, or achlorhydric patients, the investigated subjects should, of course, represent the clinical targets.

Single-Dose or Multiple-Dose Studies?

FDA and Health Canada generally suggest single-dose studies for the assessment of BE. The rationale is that of sensitive discrimination. As the FDA guidance for ANDA states (7): "We usually recommend single-dose pharmacokinetic studies for both immediate and modified release drug products to demonstrate BE because these studies are generally more sensitive than steady-state studies in assessing differences in the release of the drug substance from the drug product into the systemic circulation." The position is repeated in the NDA-IND guidance (8). (Exceptions are made when a drug substance cannot be adequately analyzed or if a single-dose study cannot be ethically undertaken.)

Calculations, simulations, and various BE studies demonstrate that the principal metrics, especially C_{max}, are contrasted more sensitively, because of the lower within-subject variation, in multiple-dose than in single-dose investigations (14–18). This is expected when, as usual, the drug release has higher variation than clearance. On the other hand, in the infrequent case when the variability of clearance is higher than that of absorption/drug release, then C_{max} would actually be higher variation in multiple- than in single-dose studies (16,18). Also, multiple-dose designs for highly variable drugs do not always reduce the within-subject variability in either AUC or C_{max} (19).

The approach of EMA is more nuanced. Single-dose investigations are recommended for drugs with immediate-release formulations except when such studies cannot be conducted in healthy volunteers due to tolerability reasons and they are not feasible in patients (9). For extended/prolonged-release preparations, however, in addition to single-dose investigations, steady-state BE studies are also required if the drug product shows accumulation when the AUC within a single dosing interval covers not more than 90% of the total, extrapolated AUC (9).

The single-dose parameters AUC and C_{max} do not, by themselves, fully characterize the steady-state concentration profiles of MR preparations. Notably, deviations between single-dose lag-times can result in differing minimum concentrations after multiple dosing. This relationship was demonstrated in an investigation of two nifedipine formulations (20). Switching within patients who are maintained on a drug product, from one product to another having a differing lag-time, can result in a strong, sudden rise or decrease of the concentration including the maximum and minimum concentrations (21).

This could be a consideration in the recommendation of EMA that an additional parameter, partial AUC, be determined for non-accumulating drugs in order to characterize the shape of the profile more appropriately.

It is noted that each of the three regulatory authorities requires that the effect of food be assessed in investigations of BE involving MR formulations.

There are further uncertainties if comparisons of single-dose concentration profiles would ensure sufficient similarity of the concentrations of MR products in the steady state and

thereby would indicate their therapeutic equivalence. For example, it was observed that the concentration recorded at the end of the intended dosing interval after single dosing is, in some cases, not sensitive to detect differences between MR products (22) as suggested earlier (23) and that multiple-dose investigations rather than single-dose studies are needed to ensure therapeutic equivalence. Also, even when two MR formulations have the same principal parameters of AUC and C_{max}, the shapes of the concentration profiles in single-dose investigations can be very different.

These considerations are particularly relevant in the case of MR formulations having multiphasic concentration profiles. It was demonstrated for formulations of zolpidem and methylphenidate that similar single-dose primary parameters did not ensure therapeutic equivalence (20,24). Therefore, FDA and EMA suggested that features of the various phases be separated and evaluated by additional metrics of partial AUCs (24–29). However, EMA suggested that cut-off times for the single-dose partial AUCs be evaluated on a case-by-case basis (30), whereas FDA expected clearly defined time-points (25,26). This has led to substantial controversies (31,32).

Altogether, the view can be questioned that single-dose studies provide most appropriate characterization of *in-vivo* product performance as the basis for the assessment of BE of MR drug products. A strong case can be made for assessing the BE of accumulating formulations as well as other PR/ER products in the steady state in order to ensure their therapeutic equivalence (33).

Peak Exposure or Index of Absorption Rate: C_{max} or C_{max}/AUC?

All regulatory authorities require for the determination of BE the comparison of two primary metrics, the area under the curve comparing plasma concentrations with time (AUC) and the maximum concentration (C_{max}).

This has been thought to be reasonable since AUC is frequently considered to be a measure of the extent of absorption, whereas C_{max} is thought to be an index of the rate of absorption (7).

Under given study conditions, AUC reflects indeed the amount of a drug reaching the systemic circulation; the ratio of AUCs of two formulations of a drug measures their relative bioavailability. The use of C_{max} as a measure of the rate of absorption is less justified. C_{max} actually reflects all processes of drug disposition. Even in the simplest (one-compartmental) case when only absorption and elimination are important, C_{max} is determined by both processes (and also by the apparent volume of distribution).

Thus, C_{max} measures only weakly the rate of absorption and the underlying absorption rate constant. In contrast, C_{max} reflects fully the extent of absorption; higher C_{max} is observed when the rate is not changed and more drug reaches the systemic circulation. Therefore, high correlation is generally expected between C_{max} and AUC under these conditions.

Consequently, it can be anticipated that by using the ratio of C_{max}/AUC, much of this correlation would be removed (34,35). Moreover, C_{max}/AUC was shown to have smaller variation than C_{max} (36). Lacey *et al.* (37) concluded from the analysis of simulated and real studies that C_{max}/AUC was more powerful than C_{max} to establish BE when the drug products were in fact bioequivalent, but also that C_{max}/AUC detected differences more sensitively when they existed.

Consequently, C_{max}/AUC exhibits more favorable properties than C_{max} as a tool of sensitive discrimination between products of different biopharmaceutic properties (and, consequently, different *in-vivo* performances). It is more specific for the evaluation of the absorption rate at least in the sense that it does not confound it with the assessment of the extent of absorption. Thus, in addition to AUC, the primary metric, C_{max}/AUC, is an effective, independent indicator of a possible deviation between two formulations. It is also a more sensitive discriminator.

On the other hand, C_{max} is primarily an indicator for drug safety (but often also of efficacy) and therefore an important therapeutic surrogate; this feature was emphasized (38,39).

As a result, the C_{max}/AUC ratio has not found so far acceptance by regulatory authorities. It was argued that C_{max} is also a measure of peak exposure (40,41) and therefore should be favored. This view has found its way to the FDA guidances (7). We would strongly suggest the reconsideration of the decision about a potential role of the C_{max}/AUC ratio.

Interestingly, another metric, obtained from the so-called intercept approach, was shown to be the most sensitive for the determination of BE for absorption rates (42,43). However, this metric has not found regulatory acceptance either.

The usual regulatory requirement is that the C_{max}'s of the two drug products should be compared. In this case, therefore, the therapeutic, clinical interpretation has been favored over the need for sensitive discrimination in product performance.

Parent Drug or Active Metabolite?

Regulatory authorities suggest that generally the parent drug rather than a metabolite should be measured in order to assess BE. The suggestion is based on considerations of sensitive discrimination as the parent drug should reflect *in-vivo* drug release more directly. For example, FDA recommends in its ANDA guidance (7) that "applicants measure only the parent drug, rather than metabolites, because the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite." Metabolites should be utilized for BE assessment only if the concentration of the parent drug is too low to allow adequate measurement in blood, plasma, or serum. EMA and Health Canada concur with this view of sensitive discrimination in product performance (9,10).

A review by Jackson *et al.* (44) notes that observations as well as simulations generally agree with the preference for using data of the parent drug. A consensus report also stated that measurement of the parent drug is the method of choice for the evaluation of BE even though the decision to use metabolite could be reached on a case-by-case basis (1). Metabolite data could be favored with drugs exhibiting linear pharmacokinetics and first-pass effect when the intra-subject variation of the first-pass metabolism is higher than the variation of the absorption process of the drug (45). Midha

et al. note that a metabolite can be a better predictor of BE than the parent drug when the intrinsic clearance is greater than liver blood flow (46). They suggest, however, that in the interests of safety, BE decision-making should be based on the parent drug whenever possible. Srinivas (47) reached the same conclusion.

In summary, EMA, FDA, and Health Canada recommend that the parent drug rather than its active metabolite should be used for the determination of BE. Thereby, they apply the view of sensitive discrimination in product performance.

DISCUSSION

Disagreements Between the Two Main Goals and Their Possible Resolution

The targeting of BE studies for both sensitive discrimination and therapeutic surrogate is reasonable and important. They feature two aspects of product performance. It is, however, of concern that their considerations and implementations are inconsistent. Such contradictions are apparent both within and between regulatory authorities (Table I).

For instance, EMA prefers good sensitive discrimination in product performance when recommending the selection of a study sample and by choosing the analysis of the parent drug over that of the metabolite. However, the clinical view is taken with the evaluation of C_{max} rather than of C_{max}/AUC and with the recommendation of multiple-dose studies for accumulating PR/ER formulations.

The priorities of FDA are also divided. The viewpoint of sensitive discrimination prevails in the expectations of single-does investigations and the analysis of the parent drug, but therapeutic, clinical considerations guide the expectation of a representative study sample and the use of C_{max}.

FDA and EMA have differing priorities in their recommendations of a study sample (clinical view and sensitive discrimination, respectively) and their suggestions for investigating MR formulations (sensitive discrimination and clinical view, respectively).

Health Canada comes closest to a consistent approach. It takes the view of sensitive discrimination in product performance except when it expects the evaluation of C_{max}.

The authors find these discrepancies and inconsistencies to be striking and therefore worthy of continuing dialogue. One could hope that regulatory authorities would be consistent in their views about the primary goal of BE studies. For instance, it would be possible that Health Canada would set a regulatory requirement not only on C_{max} but also on C_{max}/AUC. Thereby, its stance on expecting sensitive discrimination would be enhanced.

It is hoped that harmonization will proceed on the clarification and common understanding of the principal goals of BE investigations among regulatory authorities.

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