Generic Drug Product Development

International Regulatory Requirements for Bioequivalence

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INTRODUCTION

The generic drug product market is projected to grow from US $15 billion in 2004 to US $27 billion in 2009 in the United States, and from US $9 billion to US $14 billion in Western Europe (1). Moreover, the growth opportunities for generic drug products in the near future are significant with an estimated US $100 billion worth of branded pharmaceutical products to go off patent by 2010 (1). The substantial growth of the world generics drug market has been driven by a number of factors, but in particular the need to contain public health care spending, including the expenditure on drug products. In response to the important growth of the generic pharmaceutical industry during the last 10 to 15 years, regulatory agencies in countries all over the world, such as the Food and Drug Administration (FDA) in the United States, Canada's Health Products and Food Branch (HPFB), and the European Medicines Agency (EMEA) in the European Union (EU), have established requirements which must be met by a generic drug product to receive marketing authorization (2,3).

The EU offers four routes for the registration of generic drug products: (*i*) a national procedure, (*ii*) a mutual recognition procedure (MRP), (*iii*) a decentralized procedure (DCP), and (*iv*) a centralized procedure (CP) (4). The national procedure may lead to marketing authorization of the generic drug product in the concerned member state. This national procedure is still being used, but is strictly limited to medicinal products that are not authorized in more than one member state. The MRP is based on the principle of mutual recognition of national authorizations and, therefore, provides for the extension of marketing authorizations granted to one member state, the so-called reference member state (RMS), to one or more member states identified by the applicant. Since November 2005, the applicant may make use of the DCP and submit an application to each of the member states where it is intended to obtain a marketing authorization and choose one of them as the RMS. The RMS prepares a draft assessment report and collects all comments received from the concerned member states that are forwarded to the applicant. Further steps are managed by the RMS to reach a consensus and to finalize the procedure.

Since 2004, it is possible to apply for marketing authorization of medicinal products in the EU by using the CP. According to this procedure, a single

application is introduced by the applicant and is subject to a single evaluation. The scientific evaluation of this latter type of application is carried out within the Committee for Medicinal Products for Human Use (CHMP) of the EMEA and is valid throughout the EU and confers the same rights and obligations in each of the member states.[a]

Although the requirements for the approval of generic drug products may still differ among countries, one or more comparative bioavailability studies showing bioequivalence (BE) between the generic drug product and a reference product usually constitute an important part of the information requested by the regulatory agencies of most countries for marketing authorization. In addition, as for all medicinal products, the applicant must demonstrate that the manufacturing process leads to a generic product of sufficient and reproducible quality which will be maintained for the entire duration of its shelf-life.

The concept of BE and the methodology to assess BE have evolved over the past several decades. The first "European" BE guidelines were published in 1991 by the Commission of the European Communities in an attempt to harmonize the registration of generic drug products in the various member states of the European Community (EC), which has been called the EU following the Treaty of Maastricht in 1993 (5). Until the publication of this first Note for Guidance related to BE assessment, generic drug products were registered by the national authorities of the member states. In those days, the registration dossiers were not comprehensive and the assessment was based according to principles published in the scientific literature, FDA guidelines, and the first European guidelines on pharmacokinetic studies in man (6). In 1995 the EMEA, a decentralized body of the EU with headquarters in London, was established. Its main responsibility is the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use. In 2001, the EMEA Committee of Proprietary Medicinal Products (CPMP) published the current version of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (7).

This chapter provides a short overview of the EMEA Guidelines on Bioavailability and Bioequivalence studies for generic drug products and includes comments on a few of the controversial issues regarding these guidelines. Two main Notes for Guidance, prepared by the CHMP of the EMEA, are currently operational: (*i*) the Note for Guidance on the Investigation of Bioavailability and Bioequivalence that came into effect in January 2002, and (*ii*) the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation), which came into operation in January 2000 (7,8). The complete text of these guidelines can be consulted and downloaded from the EMEA website (http://www.emea.europa.eu). The objective of these guidelines is to define, for medicinal products with a systemic effect, when in vivo BE studies are necessary and to formulate requirements for their design, conduct, and evaluation. After the current Note for Guidance on

[a] Norway, Iceland and Liechtenstein form the European Economic Area (EEA) with the 25 member states of the EU. These countries have, through the EEA agreement, adopted the complete EU acquis on medicinal products and are consequently parties to the EU procedures. Where in this text reference is made to member states of the EU this should be read to include Norway, Iceland and Liechtenstein.

the Investigation of Bioavailability and Bioequivalence came into effect (January 2002), it appeared that some harmonization regarding the interpretation of critical parts of the guideline was needed. As a result, a Questions & Answers document was published in 2006 by the CHMP Efficacy Working Party (EWP), which clarifies some of the critical parts of this EMEA guidance (9). A revised version of the current BE guidelines for oral, immediate release drug products with systemic action has been in preparation for some time by the CPMP efficacy working party on pharmacokinetics (EWP-PK) of the EMEA. The draft version of this revision of the BE guidelines, entitled Guideline on the Investigation of Bioequivalence, was made publicly available in August 2008 on the EMEA website and a modified version will probably come into effect in 2010 (10).

The application for marketing authorization of a generic drug product, the so-called "generic" application, is an abridged application because the applicant is neither required to provide the results of pharmacological or toxicological tests nor the results of clinical trials if it can be demonstrated that the medicinal product is essentially similar to a product that has been authorized within the community (i.e., the member states of the EU plus Norway, Iceland, and Liechtenstein) for not less than 6 to 10 years and is marketed in the member state for which the application is made (4). According to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence (7):

> 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.

The Note for Guidance further explains (7)

> 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.

As pointed out in the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence, demonstration of BE is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, but for pharmaceutical alternatives containing a different salt or ester of the active substance, additional safety data may be needed in some cases (7,11).

ORAL IMMEDIATE RELEASE DOSAGE FORMS WITH SYSTEMIC ACTION

BE studies are clinical studies involving human subjects and, therefore, must follow regulations on good clinical practice (GCP). The design, conduct, and evaluation of BE studies for oral immediate release dosage forms intended to act, following absorption of the active moiety into the systemic circulation are described in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (7). In what follows, a brief description of the important aspects of BE studies for oral immediate release dosage forms as laid out in this guidance will be presented together with some critical comments and comparisons with the BE guidelines of other countries such as Canada and the United States. Where

necessary, reference will be made to the new revised EMEA Guideline on the Investigation of Bioequivalence but it should be kept in mind that, at this stage, it is only a draft version (10).

Study Design

For many drugs a large intersubject variability in pharmacokinetic parameters, such as the extent of absorption (*F*), the apparent volume of distribution (*V*), and plasma clearance (CL), is generally observed. The intrasubject variability usually is substantially smaller than the between-subject or intersubject variability and, therefore, a cross-over design is generally recommended for BE studies (12,13). The EMEA Note for Guidance on the Investigation of Bioequivalence and Bioavailability is clear in this regard and recommends a two-period, two-sequence cross-over design, with random allocation of the subjects to each sequence, when comparing the bioavailability of two medicinal products (7). Other study designs may be acceptable, such as a parallel study design for long half-life substances and replicate designs for substances with highly variable pharmacokinetics (14). In the case of a cross-over design, treatments should be separated by a sufficiently long washout period (usually at least five times the terminal plasma half-life of the active drug substance or its metabolites) to ensure that all of the drug and/or its metabolite(s) has been cleared from the body prior to the time of the subsequent administration.

The number of subjects required for a BE study should ideally be estimated at the design stage and is determined by (*i*) the error variance (σ^2) of the primary BE metrics to be studied, (*ii*) the significance level (α), (*iii*) the expected deviation, with respect to the primary BE metrics, between the two formulations which is considered compatible with BE (e.g., ± 20% for AUC), and (*iv*) the required statistical power (15,16). An estimate of the error variance can be obtained from the published literature, a previous BE study, or by undertaking a pilot study. Nomograms of the number of subjects required for various ratios of the expected means for test and reference products and various intrasubject coefficients of variation have been published by Diletti et al. (15,17). The guidance document of Canada's HPFB allows an add-on study (stated a priori in the protocol) when the results from the first study fail to reach the required power, under the condition that appropriate statistical tests validate the analysis of the combined data (18). The draft version of the revised EMEA Guideline on the Investigation of Bioequivalence includes a recommendation regarding under which circumstances a sequential design (a so-called two-stage approach) may be used (10).

For oral immediate release dosage forms the EMEA guidance favors a study where a single dose is taken on an empty stomach, that is, following an overnight fast, with a fixed volume of fluid (at least 150 mL). However, if it is recommended in the summary of product characteristics (SPC) that the reference medicinal product should be taken with a meal, the BE study should be carried out under fed conditions if the recommendation of food intake has any pharmacokinetic implications such as a higher bioavailability (9). All subsequent meals and drinks as well as other test conditions (e.g., posture during the first few hours following intake of the medicinal products, physical activity, etc.) should be standardized to minimize the variability in the bioavailability metrics unrelated to a possible difference in the formulations. For the same reason of minimising variability, BE studies are recommended to be carried out in healthy

volunteers, of either sex, between 18 and 55 years old having a normal body weight based on body mass index, preferably nonsmokers, and without a history of alcohol or drug abuse. For an active substance known to be subject to major genetic polymorphism in its metabolic elimination, phenotyping/genotyping "should be considered" according to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence when using a parallel design (7). Phenotyping/genotyping "may be considered" as well for crossover BE studies for safety or pharmacokinetic reasons (7). Indeed, plasma concentrations of an active substance that is a substrate for an enzyme showing genetic polymorphism may be much higher and half-lives much longer in poor metabolizers, thus necessitating longer sampling schedules compared to extensive metabolizers (19).

Although, in general, a single-dose study will suffice to show that a generic drug product is bioequivalent to an approved reference product, according to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence there are situations in which steady-state studies may be required or can be considered (7). These situations may include BE studies for active substances undergoing dose- or time-dependent kinetics, or for active substances with high intraindividual variability for which it may be difficult or even impossible to demonstrate BE in a reasonably sized single-dose study. In addition, steady-state studies can be considered when problems of analytical sensitivity preclude sufficiently precise measurement of analyte plasma concentrations after single-dose administration. According to the revised EMEA Guideline on the Investigation of Bioequivalence, a multiple-dose study as an alternative to a single-dose study may also be acceptable if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single-dose administration. However, if possible, C_{max} should be determined as a measure of peak exposure following administration of the first dose of the multiple-dose study. AUC, a measure of extent of exposure, should be determined at steady state. Moreover, in a multiple-dose BE study the administration scheme should preferably follow the highest usual dosage recommendation (10).

Post hoc exclusion of outliers based on pharmacokinetic or statistical reasons alone is not accepted (7,9). Nonstatistical reasons to exclude the data of a particular subject from the final statistical analysis should have been prospectively defined in the protocol, or according the EMEA Questions & Answers document on the bioavailability and BE guideline: "... at the very least, established before reviewing the data." Acceptable explanations to exclude pharmacokinetic data or to exclude a subject from the final statistical analysis would be protocol violations such as vomiting, diarrhoea, analytical failure, etc.

Reference and Test Products

In a BE study which is carried out as part of an application for marketing authorization of a generic medicinal product, the bioavailability of the generic product (test) is compared to the bioavailability of an innovator medicinal product (reference). The batches of the test and reference product used in the BE study are called the "biobatches." The requirements for the test product used in the BE study are clearly spelled out in the EU guidance. 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. As far as the reference product is concerned, the EMEA guidance specifies that the choice of the reference product should be justified by the applicant. The reference product should normally be the innovator, a medicinal product authorized on the basis of a full dossier. When the innovator is no longer on the market, the product that is the market leader may be used as the reference product provided that it has been authorized for marketing and its efficacy, safety, and quality have been fully established and documented. In the case of a MRP, application for marketing authorization to numerous member states based on a BE study with a reference product from one member state, that is, the RMS, can be made. In general, the qualitative and quantitative composition of the reference product is the same in all the member states of the EU. However, if the reference products marketed in the various member states slightly differ in terms of qualitative/quantitative composition of the excipients as well as the manufacturing process, extrapolation of the results of the BE study carried out with the reference medicinal product marketed in one particular member state to BE claims in comparison to reference products marketed in the other member states is not always straightforward. Comparative in vitro dissolution profiles between the reference product used in the BE study and the one registered and marketed in the member state where marketing authorization is requested may be asked by the assessors. The in vitro dissolution method should be discriminating and in accordance with the pharmacopoeial requirements. The in vitro dissolution profiles may be compared by calculating an f_2 similarity factor. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. Alternative methods to prove similarity of dissolution profiles are accepted as long as they are justified. In cases where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles are considered to be similar without further mathematical evaluation. In cases where the composition and/or the manufacturing process of the reference product used in the BE study compared to the reference product registered and marketed in the member state(s) where marketing authorization is requested differ to such an extent that the bioavailability may be affected, a BE study with the latter may be requested. The EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence, however, is not very helpful in this regard:

> 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.

Indeed, no indication whatsoever is given as to the nature and/or importance of the differences in composition and manufacturing process between reference products marketed in the various member states that would necessitate a new BE study. Perhaps a series of guidelines such as those issued by the FDA in the case of scale-up and postapproval changes (SUPAC) would be helpful to decide when an additional BE study between the generic product versus the reference medicinal product registered in a particular concerned member state would be required (20). Although the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence suggests that in vitro dissolution

studies can be used as "bioequivalence surrogate inference" to demonstrate similarity between the reference products from different member states, they cannot replace for most active substances an in vivo BE study unless an in vitro/in vivo correlation (IVIVC) has been demonstrated (21,22).

BE Metrics

The area under the plasma (serum, blood) concentration of the parent compound versus time curve (AUC_t, AUC_∞) generally serves as a measure of the extent of absorption. T_{max} and the corresponding maximum plasma concentration, C_{max}, may serve as characteristics of the rate of absorption. However, it should be emphasized that C_{max} is not a pure measure of absorption rate but is confounded with the extent of absorption (23). Urine excretion data may also be used to determine the extent of absorption provided elimination is predominantly renal as intact drug substance and is dose proportional (7,9). In the revised EMEA Guideline on the Investigation of Bioequivalence the condition that "elimination is dose-linear and is predominantly renal as intact drug" is no longer mentioned (10). However, the use of urinary data has to be carefully justified when used to estimate the rate of absorption (9,10,24).

AUC_∞, the area under the curve extrapolated to infinity, can only be reliably measured if the terminal plasma half-life can be accurately determined, which is not always the case. AUC_t, the area under the curve from the time of administration to the last measurable plasma concentration at time t, is therefore considered to be the most reliable measure of the extent of absorption provided that it covers at least 80% of AUC_∞. Literature data support the notion that BE assessment for long half-life drugs is not adversely affected by using truncated AUC (25–29). Blood sampling time in this case should be sufficiently long to ensure completion of gastrointestinal transit of the drug product (approximately two to three days) and consequently the absorption process of the drug substance. The Canadian HPFB guidelines, for example, accept AUC_{0-72}, the AUC from time 0 to 72 hours following administration, as a measure of extent of absorption for drug substances with a half-life of more than 12 hours (30).

Moiety To Be Measured: Parent Drug Versus Metabolite(s)

In most cases the evaluation of BE should be based on the measurement of plasma concentrations of the parent compound. The rationale for this approach is that the concentration–time profile of the parent drug is more sensitive to changes in formulation performance than that of the metabolite, which includes the processes of metabolite formation, distribution and elimination. However, according to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence: "In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound." A clear consensus on the role of metabolites for the assessment of BE has not yet been achieved within the scientific community (31–33). This is reflected in the different views expressed in the current national and international regulatory guidelines concerning the role of the measurement of metabolites in BE assessment. According to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence, measurement of metabolites is required to assess BE between two medicinal products in the following cases: (*i*) if the

concentration of the parent compound is too low to be accurately measured and *(ii)* if the parent compound is unstable in the biological matrix or its half-life is too short (7). The same guidelines further state:

> 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 and evaluate them separately.

The most recent version of the general BE guidance from the FDA requests that only the parent compound should be measured to assess BE (34). Only when a metabolite is formed as a result of gut wall or other presystemic metabolism and the metabolite contributes to safety and efficacy is the metabolite measured to provide supportive evidence. In all other instances only the parent compound is measured for BE. According to the guidelines of Canada's HPFB, the determination of BE is based on measurement of the active ingredient, or its metabolite, or both, as a function of time (18). They further specify that normally measurement of the parent compound is sufficient but in some cases measurement of the metabolite could be required. For example, when a prodrug is administered, the active metabolite should be measured. The Questions & Answers document on the Bioavailability and Bioequivalence Guideline which were recently formulated by the CHMP Efficacy Working Party of the EMEA, also deals with the issue when metabolite data should be used to establish BE (9). This document stipulates that metabolite data can only be used if the applicant presents state-of-the-art evidence that measurements of plasma concentrations of the parent compound are unreliable. In addition, it is pointed out that C_{max} of the metabolite is less sensitive to differences in the rate of absorption than C_{max} of the parent compound:

> Therefore, when the rate of absorption is considered of clinical importance, bioequivalence should, if possible, be determined for C_{max} of the parent compound if necessary following administration of a higher dose. (9)

In their excellent review of the topic of measurement of metabolites for BE assessment, Jackson et al. conclude that the parent compound is the entity most sensitive to formulation changes (31,33). The continuing belief by some that activity is important and should be considered for BE assessment is the major reason for most of the controversy regarding metabolite measurement. Another argument for using metabolites in BE assessment is that metabolite concentrations are generally associated with a lower intrasubject variability and consequently their use allows a decrease in the number of subjects required to establish BE. However, analysis of both parent drug and metabolite to assess BE is problematic since it would decrease Type I error (consumer risk) and increase Type II error (producer risk) (33).

Calculation of Confidence Interval and Acceptance Limits

Estimation of BE is based on the "two one-sided tests" procedure (35) in which the 90% confidence interval (CI) around the geometric mean ratio of the test and reference values of an appropriate bioavailability measure, such as AUC or C_{max}, is required to fall within preset BE limits. One of the important objectives of BE testing is to assure that two medicinal products containing the same

active substance are interchangeable in any individual patient. For this reason, the "two one-sided tests" procedure is based on the intrasubject variability that is commonly estimated from the mean square error (MSE), also called the residual mean square, of an analysis of variance in which the fixed effects are typically formulation, period, sequence, and subject nested within sequence. The intrasubject variability can be estimated from the MSE by calculating the CV_{anova} (ANOVA coefficient of variation) as follows:

$$CV_{anova}(\%) = \left(\sqrt{e^{MSE} - 1}\right) 100$$

The width of the 90% CI depends on the magnitude of MSE and the number of subjects in the BE study. Active substances whose AUC and C_{max} show a high intrasubject variability have high values for CV_{anova} (>30%) and are called highly variable drugs (HVDs). The larger the CV_{anova}, the higher the number of subjects required to give adequate statistical power (16,17).

The usual acceptance limit for the 90% CI around the geometric mean ratio for AUC and C_{max}, that is, 0.80 to 1.25 (or 80–125%), is based on a consensus amongst clinical experts that a difference of ±20% in plasma concentrations of the active substance following administration of two different medicinal products would have no clinical significance for most drugs (36). Since measures derived from plasma concentrations such as AUC and C_{max} are log-normally distributed, this ±20% translates into an asymmetric acceptance limit, for example, 0.80 to 1.25. The EMEA Note for Guidance suggests that in specific cases of active substances with a narrow therapeutic index (NTI) the acceptance interval may need to be tightened but does not give more specific information (7). The draft version of the EMEA revised Guideline on the Investigation of Bioequivalence adds that "... the need for narrowing the acceptance interval for both AUC and C_{max} or for AUC only should be determined on a case by case basis." (10)

The HPFB of Canada has issued Guidance for Industry on the bioequivalence requirements for critical dose drugs (37). According to this guidance, "critical dose drugs" are defined as those drugs for which comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions. For these "critical dose drugs," the 90% CI of the relative mean AUC of the test to reference formulation should lie within 90% to 112%, according to Canada's HPFB guidance. In addition, the 90% CI of the relative mean C_{max} of the test to reference formulation for these "critical dose drugs" should be between 80% and 125%. For "uncomplicated" drugs, Canada's HPFB requires the point estimate of C_{max} to simply lie between 80% and 125%. These requirements for "critical dose drugs" are to be met in both the fasted and fed states. In an appendix to this HPFB guidance a list of 9 "critical dose drugs" is given (37). The FDA Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products recommends that the usual BE limit of 80% to 125% for non-NTI drugs remain unchanged for the bioavailability measures (AUC and C_{max}) for NTI drug substances unless otherwise indicated by a specific guidance (34).

On the other hand, wider BE limits for the 90% CI may be acceptable for C_{max} (in certain cases) and for AUC (in rare cases) according to the EMEA Note for Guidance (7). Indeed, when the intrasubject variability in AUC and C_{max} is high the estimated 90% CI is wide and it is very difficult to be entirely located

within the usually accepted BE limits of 0.80 to 1.25. Among the methods proposed during recent years in the scientific literature to evaluate the BE of these highly variable drugs and drug products, scaled average BE and expanding the usual BE limits to, for example, 0.75 to 1.33, were recently shown to be sensitive to differences between means and, consequently, highly effective for assessing the equivalence of average kinetic responses (38–40). Recently, a commentary was published in which the authors proposed to adjust the BE limits for highly variable drugs/drug products by scaling to the intrasubject variability of the reference product in the study (41). The recommendation for the use of reference scaling is based on the general concept that reference variability should be used as an index for setting the public standard expressed in the BE limit. The use of the reference-scaling approach necessitates a study design that evaluates the reference variability via replicate administration of the reference product to each subject.

BE studies using a replicate design, for example a three-period or four-period study, have certain advantages over the classical two-period design. They allow the comparison of the intrasubject variance and the evaluation of the subject-by-formulation interaction. Information on these variances associated with the test and reference formulations allows assessment of the pharmaceutical quality of a new test product compared to the pharmaceutical quality of the marketed innovator product. At the moment, none of the major health authorities (EMEA, FDA, HPFB), however, provide clear recommendations on how to assess BE of highly variable drugs or drug products.

The draft version of the revised EMEA Guideline on the Investigation of Bioequivalence is clear in this respect. According to this guideline, it is acceptable to widen the 90% acceptance range of C_{max}, but not AUC, from 0.80–1.25 to 0.75–1.33 under the following conditions: (*i*) the 0.75 to 1.33 acceptance range has been prospectively defined in the study protocol, (*ii*) it has been prospectively justified that widening of the acceptance criteria for C_{max} does not affect clinical efficacy or safety, and (*iii*) the BE study is of a replicate design where it has been demonstrated that the intrasubject variability for C_{max} of the reference compound in the study is >30% (10).

Exemptions from In Vivo BE Studies (Biowaivers)

The biopharmaceutics classification system (BCS) provides a scientific framework for classifying active substances based on their aqueous solubility and intestinal permeability (21,42,43). When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account the major factors, that is, solubility and intestinal permeability, which are fundamental in controlling the rate and extent of oral drug absorption from immediate release solid oral dosage forms. In August 2000, the FDA issued a guidance for industry on waivers of in vivo bioavailability and BE studies for immediate release solid oral dosage forms (44). This guidance recommends that applicants may request biowaivers for highly soluble and highly permeable drug substances (BCS class I) in immediate release solid oral dosage forms provided that they exhibit rapid in vitro dissolution rates and a few other conditions are met. The methods for determining solubility, permeability, and in vitro dissolution are described in this FDA biowaiver guidance as well as the approaches recommended for classifying drug substances according to the BCS.

The EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence under certain conditions also allows exemptions from in vivo BE studies for oral immediate release dosage forms with systemic action (7). Although this exemption from in vivo BE studies is based on similar considerations as those described in the FDA Guidance for Industry (44), the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence is much less detailed in the description of the criteria on which a biowaiver may be granted. Biowaivers are still rarely used in the EU probably due to uncertainties by both the pharmaceutical companies and the regulatory authorities regarding the application of the biowaiver principles. An example of a biowaiver, accepted by the German regulatory authority, that is, the Bundesinstitut für Arzneimittel und Medizinprodukte in Bonn, has been described in the scientific literature for 80 and 160 mg immediate release tablets containing sotalol hydrochloride, a BCS class I substance (45). To reach an optimal and harmonized application based on biowaiver principles, the draft version of the revised EMEA Guideline on the Investigation of Bioequivalence addresses the issue of BCS-based biowaivers in much more detail than the current EMEA Note for Guidance (10,46). According to this revised EMEA Guideline on the Investigation of Bioequivalence, BCS-based biowaivers will be considered not only for BCS class I drug substances (high solubility, high permeability), but also for BCS class III substances (high solubility, low permeability), as has been proposed in multiple scientific commentaries (47–49). In the latter case, special attention will have to be paid to the excipients since it is known that the absorption of BCS class III substances is more susceptible to transporter-mediated excipient–drug interactions (50,51).

Formulation Changes and Variations

Information to document BE following reformulation of an approved generic (or innovator) drug product or following a modification in its manufacturing process or manufacturing equipment used is obviously required. Volume 2 of the publication "The rules governing medicinal products in the European Union" contains a list of regulatory guidelines related to procedural and regulatory requirements such as renewal procedures, dossier requirements for variation notifications, summary of product characteristics, package information, readability of the label, and package leaflet requirements (51). Since 2003, new categories of variations, that is, notifications type IA and type IB, have been introduced in the EU (52). Type IA variations are "minor" variations, for example, a change in the name and/or address of the marketing authorization holder, a change in the name of the active substance or its ATC (anatomical therapeutic chemical) code, which do not require a new in vivo BE study. Examples of type IB notifications are a minor change in the manufacturing process of the active substance, a minor change in the manufacturing process of the finished product, replacement of an excipient with a comparable excipient. For some type IB notifications, a justification for not submitting a new BE study and/or comparative dissolution data must be provided. Type II variations constitute "major" changes and an in vivo BE study is required unless a biowaiver can be granted on the basis of in vitro dissolution tests (BCS-based biowaiver, in vitro–in vivo correlation).

Unlike the FDA, which has a specific guidance on SUPAC, the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence only has a small paragraph on 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 . . ., or on whether an acceptable in vivo/in vitro correlation has been established. (7).

From a regulator's and sponsor's point of view it would be desirable to have clear and more detailed guidelines on this important issue, such as the SUPAC guidelines of the FDA, to guarantee the continuing quality of a generic drug product even during the postapproval period.

Bioequivalence of Chiral Drugs

Attempts have been made in the scientific literature to examine the stereochemical aspects of BE and several examples demonstrate that BE between two medicinal products containing a mixture of stereoisomers based on non-stereospecific assays alone may not be extended to the pharmacologically relevant stereoisomer(s) (53–55). The results of these studies suggest that stereospecific assays are necessary for at least some chiral drugs. However, at this time no consensus has been reached regarding the conditions whereby BE of medicinal products containing a mixture of stereoisomers should be assessed (56). According to the current EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence:

> . . . bioequivalence studies supporting applications for essentially similar medicinal products containing chiral active substances should be based upon enantiomeric bio-analytical methods unless (1) both products contain the same stable single enantiomer; (2) both products contain the racemate and both enantiomers show linear pharmacokinetics.

The draft version of the revised EMEA Guideline on the Investigation of Bioequivalence provides much clearer recommendations on this issue (10).

Locally Applied Drug Products

According to the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence, for drug products for local use (oral, nasal, ocular, dermal, rectal, vaginal, inhalation, etc.) intended to act without systemic absorption the approach to assess BE on the basis of systemic concentrations of the active substance is not applicable and pharmacodynamic or comparative clinical studies are in principle required (7,57).

The EMEA is currently working on a detailed guideline describing the requirements for clinical documentation for abridged applications for orally inhaled formulations and variations/extensions to a marketing authorization with respect to demonstrating therapeutic equivalence between two inhaled products for use in the management and treatment of asthma and chronic obstructive pulmonary disease (58).

As far as the assessment of therapeutic equivalence between topical corticosteroid products is concerned, the current EMEA guidance in question has been in operation since 1987 (59). More recently, a Questions & Answers

document was released by the EMEA dealing more specifically with the vasoconstriction (human skin blanching) assay that may reduce the need for data from clinical trials when assessing therapeutic equivalence between topical corticosteroid products (60). This document refers to the FDA guidance for industry for a detailed description of how to perform this vasoconstriction assay (61).

MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS

In January 2000, the EMEA Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) came into effect (8). The primary purpose of this guidance was

> to define the studies necessary to investigate the properties and effects of the new delivery system in man and to set out general principles for designing, conducting and evaluating such studies.

Although the guidance only deals with oral modified release formulations and transdermal dosage forms, most recommendations are also applicable to implants and intramuscular/subcutaneous depot formulations. Paragraph 5 of this document specifically deals with applications for modified release dosage forms essentially similar to a marketed modified release form, that is, so-called generic applications. A distinction is made between prolonged release oral formulations, delayed release oral formulations and transdermal drug delivery systems (TDDS).

Prolonged Release Oral Formulations

Whereas BE for oral immediate release dosage forms with systemic action is established on the basis of a single-dose study usually carried out in the fasting state, the EMEA Note for Guidance on Modified Release Oral and Transdermal Dosage Forms recommends that assessment of BE of prolonged release oral formulations should be based on single- *and* multiple-dose studies. Typically, single- and multiple-dose studies are carried out with the test and reference formulation following an overnight fast. In addition, a single-dose study has to be carried out with both test and reference formulation administered after a predefined high-fat meal. The effect of this high-fat meal on the in vivo bioavailability should be comparable for both preparations. The conditions to apply for a biowaiver in case the application concerns multiple strengths are different for single unit and multiple unit prolonged release oral formulations (8). It is interesting to note that the FDA guidance recommends only single-dose studies (a fasting study and a food-effect study) for modified release products submitted as Abbreviated New Drug Applications (ANDA) (34). Their argument is that single-dose studies are more sensitive to assess BE between two drug products. Canada's HPFB guidelines for BE assessment on oral modified release formulations also recommend single-dose BE studies under fasting and fed conditions. In addition, for formulations that are likely to lead to accumulation of the active substance in plasma, the HPFB also recommends a BE study at steady state, that is, after multiple-dose administration (62).

According to the EMEA Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: "Assessment of bioequivalence will be based on AUC_τ, C_{max}, and C_{min} applying similar statistical procedures as for the immediate release formulations." However, in the case of prolonged release formulations, which at steady state may show relatively flat plasma concentration–time

curves often with multiple peaks, C_{max} is of limited value to characterize the rate of absorption. Therefore, other measures such as the half-value duration, peak-trough fluctuation (PTF), and percent swing may be useful alternatives (63,64). Any widening of the usual 0.80 to 1.25 acceptance criterion should be prospectively established in the study protocol and should be clinically justified.

Delayed Release Oral Formulations

An enteric-coated formulation, the most common example of a delayed release formulation, is designed to protect the active substance from the acid environment of the stomach or to protect the stomach from the active substance. The EMEA Note for Guidance on Modified Release Oral and Transdermal Dosage Forms only specifies for this particular case of a modified release oral dosage form that (*i*) BE is assessed using the same main characteristics and statistical procedures as for immediate release oral formulations and (*ii*) postprandial bioequivalence studies are necessary. It is not clear, though, whether only a food-effect study has to be carried out, or whether in addition a fasting study is recommended (8).

Transdermal Drug Delivery Systems

A TDDS or transdermal patch is defined as a flexible pharmaceutical preparation of varying size containing one or more active substances to be applied on the intact skin to provide a slow delivery of the active substance(s) into the systemic circulation. Transdermal patches are often highly variable drug products and consequently BE studies with replicate designs are recommended by the EMEA Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (8). A replicate study is required if the systemic bioavailability of TDDS with different release mechanisms, for example, reservoir versus matrix, is compared because this design allows the assessment of the subject-by-formulation interaction. In general, the BE of TDDS should be assessed after single-dose and multiple-dose administration. When the application for marketing authorization concerns multiple strengths of a TDDS, BE studies can be performed on the highest strength only provided certain conditions are met such as (*i*) the strength is proportional to the effective surface area of the TDDS, and (*ii*) an acceptable in vitro release test exists. Finally, test product and reference product should demonstrate the same (or less) degree of local irritation, phototoxicity, sensitization and systemic adverse events, and a similar degree of adhesiveness to the skin. Although the EMEA guidance does not further elaborate on this last point, the FDA has published a guidance for industry specifically treating skin irritation and sensitization testing of generic transdermal drug products (65).

FIXED COMBINATION DRUG PRODUCTS

For fixed combination drug products, in vivo BE should be evaluated for each individual active substance. The study design and BE assessment methodology and criteria are the same as those applied to oral immediate release formulations. The reference product used in the BE study should be the originator fixed combination product (7).

A Questions & Answers document was released by the EMEA in 2005 regarding the clinical development of fixed combinations of drugs belonging

to different therapeutic classes in the field of cardiovascular treatment and prevention (66). This "guideline" discusses what is required in case a new combination product is developed of active substances as substitution therapy for patients adequately controlled with the same active substances given concurrently at the same dose level and dosing interval but as separate single-substance drug products. In this particular case, only BE should be demonstrated between the already existing single-substance drug products and the fixed combination drug product according to the recommendations described in the EMEA Note for Guidance on the Investigation of Bioavailability and Bioequivalence (7). The possibility that the active substances may interact pharmacokinetically should be documented.

CONCLUSION: TOWARD GLOBAL HARMONIZATION?

The generic drug approval process has evolved over the past 30 years and regulatory agencies in a number of western countries have now established stringent requirements for the design, performance and evaluation of BE studies to protect the consumer of being exposed to drug products of inferior quality. Although the current BE guidelines and recommendations of the major regional and national health authorities show a fair degree of consistency, a number of outstanding BE issues and concerns remain to be resolved. The most obvious of these controversial issues, such as the BE acceptance limits for NTI drugs and HVDs, the role of metabolites in BE assessment, the use of stereospecific bioanalytical assays to determine BE of chiral drugs, the choice of the reference product, conditions to grant biowaivers, are not dealt with in the same way by the various guidelines. For example, the World Health Organization (WHO), which is not a regulatory body but publishes technical reports and guidelines that are recommendations to national authorities especially in developing countries, not only allows biowaivers for BCS class I substances but also allows biowaivers under certain circumstances for class II and class III substances (67). At this moment, the FDA and the EMEA do not allow biowaivers for BCS class II substances (68). This creates confusion that in turn leads to suspicion by health care providers and patients, especially since many national authorities give these WHO reports regulatory status. All stakeholders in the development and registration of new drug products must balance the need for scientific rigor in assuring BA/BE (and hence product quality toward consistent therapeutic outcomes) with the time and expense of conducting in vivo BE studies, and the overall impact on product costs and timely availability to patients. Ideally these guidelines should be the same worldwide to ensure that patients all over the world can benefit from affordable and safe medicinal products.

Global harmonization should therefore be the next logical step in the continuing process to improve the BE guidelines as a means to guarantee safe and efficacious drug products for the consumer in all parts of the world. Global harmonization efforts by the International Conference on Harmonization (ICH) and the WHO should be stepped up in collaboration with the regulatory agencies of the western world as more nations throughout the world have come to rely on low-cost, good-quality multisource (generic) pharmaceutical products as means of providing lower health care costs without sacrificing important public health goals. However, as already pointed out, a consensus on a number of BE issues has not even been reached at this point in time among international regulatory

agencies. In addition, differing levels of commitment and resources by the various countries and regions constitute another formidable barrier that has to be overcome to harmonize BE approaches to ensure development of optimally performing and affordable drug products for use by health practitioners and patients in he global community.

NOTE ADDED IN PROOF

The following important Questions & Answers document was published after completion of the manuscript: "Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics", EMEA/618604/2008 Rev. 1, London, 23 July 2009. http://www.emea.europa.eu/pdfs/human/ewp/61860408en.pdf (accessed on November 9, 2009).

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