Meeting Report

Harmonization of Regulatory Approaches for Evaluating Therapeutic Equivalence and Interchangeability of Multisource Drug Products: Workshop Summary Report

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Abstract. Regulatory approaches for evaluating therapeutic equivalence of multisource (or generic) drug products vary among different countries and/or regions. Harmonization of these approaches may decrease the number of *in vivo* bioequivalence studies and avoid unnecessary drug exposure to humans. Global harmonization for regulatory requirements may be promoted by a better understanding of factors underlying product performance and expectations from different regulatory authorities. This workshop provided an opportunity for pharmaceutical scientists from academia, industry and regulatory agencies to have open discussions on current regulatory issues and industry practices, facilitating harmonization of regulatory approaches for establishing therapeutic equivalence and interchangeability of multisource drug products.

KEY WORDS: bioequivalence; harmonization; interchangeability; regulatory standards; therapeutic equivalence.

INTRODUCTION

This report provides a summary of the workshop entitled “Harmonization of Regulatory Approaches for Evaluating Therapeutic Equivalence and Interchangeability of Multisource and Complex Drug Products” held on November 13–14, 2010, New Orleans, Louisiana, USA. The workshop was co-sponsored by the American Association of Pharmaceutical

Scientists (AAPS), European Federation of Pharmaceutical Sciences (EUFEPS), and International Pharmaceutical Federation (FIP).

The generic pharmaceutical industry has become increasingly more global and is manufacturing multisource drug products for both domestic and international markets. Multisource drug products are products marketed by more than one manufacturer that contain the same active pharmaceutical ingredient (API) or drug substance in the same dosage form, the same strength and are given by the same route of administration (1,2). Designation of multisource (or generic) drug products as therapeutic equivalents to a reference drug product (usually the brand product) requires regulatory approval. However, approaches for regulatory approval of these drug products vary among different regions and/or countries, which in some cases, may render additional bioequivalence studies necessary to meet the requirements of each of these regulatory agencies. Ideally, harmonization of regulatory requirements would decrease the number of *in vivo* bioequivalence studies, avoid unnecessary drug exposure to humans, and reduce the cost of generic drug development. Global harmonization for the regulatory requirements may be promoted by a better understanding of factors underlying product performance and expectations from different regulatory authorities. Accordingly, the goals and objectives of this workshop were to:

1. Review scientific and regulatory approaches for demonstrating pharmaceutical equivalence and bioequivalence of multisource drug products from different regions and/or countries

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2. Discuss existing and emerging issues in determining therapeutic equivalence of drug products
3. Examine current bioequivalence methods and criteria using pharmacokinetic measures and pharmacodynamic/clinical endpoints for various dosage forms, including highly variable drug products
4. Discuss the selection of reference listed drugs (RLDs) for multiple jurisdictions and challenges in conducting *in vivo* bioequivalence studies for global market
5. Examine available *in vitro* methods for bioequivalence assessment, and identify potential *in vitro*–*in vivo* correlations for biowaivers
6. Explore ways to harmonize regulatory requirements for demonstrating therapeutic equivalence and interchangeability of multisource products

The 2-day workshop provided an opportunity for pharmaceutical scientists from academia, industry and regulatory agencies to have open discussions on current regulatory issues and industry practices, facilitating harmonization of regulatory approaches for establishing therapeutic equivalence and interchangeability of multisource drug products.

This summary report highlights the presentations and recommendations discussed at the workshop. Note that the current report only focuses on multisource drug products and does not include complex drugs, biosimilars or biological products. Complex drug products such as iron–sucrose complexes, peptide mixtures, and low-molecular-weight heparins were discussed at the workshop. However, equivalence evaluation of these products is much more complicated, requiring further development of standards and criteria by the regulatory authorities.

REGULATORY APPROVAL OF MULTISOURCE DRUG PRODUCTS

According to the World Health Organization (WHO), multisource or generic drug products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent (1). Multisource pharmaceutical products that are both pharmaceutically equivalent and bioequivalent (thus therapeutically equivalent) are considered interchangeable. Documentation of therapeutic equivalence may be shown directly or indirectly by various test methods deemed suitable by regulatory authorities. Among these, determination of bioequivalence is the most important for therapeutic equivalence, which is also the most difficult part of generic drug product development. There is a universal agreement that bioequivalence testing should use the most accurate, sensitive, and reproducible approach available for the drug product under examination. The following methods have been recommended for bioequivalence testing: (a) comparative pharmacokinetic studies in humans, (b) comparative pharmacodynamic studies in humans, (c) comparative clinical trials, and (d) comparative *in vitro* tests. In practice, pharmacokinetic approaches that compare drug concentrations in blood/plasma versus time profiles are mostly used for bioequivalence demonstration. Pharmacodynamic or clinical equivalence studies are employed only when appropriate pharmacokinetic studies are not feasible to perform (e.g., bioanalytical methods are either unavailable or insufficiently sensitive for measurement of a drug

or its metabolite(s) in accessible biological fluids), and/or are not discriminatory of product performance at the site of activity (e.g., drug concentrations in blood/plasma do not reflect drug availability at the site of action). *In vitro* studies, such as comparative drug dissolution/release testing, may be used on a “stand-alone” basis for certain drugs that meet the biowaiver criteria based on the Biopharmaceutics Classification System (BCS). In the US, these include Class 1, highly soluble and highly permeable drugs (3). In the European Union (EU) and the WHO guideline, biowaiver criteria have been extended to Class 3, highly soluble and incompletely absorbed drugs, under special conditions (1,4). The WHO guideline also has a provision for certain Class 2 drugs (that are highly soluble at pH 6.8) to be considered for biowaiver approval (1).

IN VIVO BIOEQUIVALENCE STUDIES

Comparative Pharmacokinetic Studies

Table I provides a comparison of various regulatory requirements in different countries or regions for *in vivo* bioequivalence studies using pharmacokinetic measures (1,3–9). Note that this table is only for orally administered drug products with systemic action. As shown, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada (HC), and WHO have similar bioequivalence requirements for conduct of *in vivo* pharmacokinetic studies, with variations in some details. For example, bioequivalence testing is commonly performed as a single-dose, two-period, cross-over study in healthy volunteers. Multiple-dose (steady-state) studies or parallel designs in patients may be employed as appropriate. It should be noted that the HC has issued two draft guidances on comparative bioavailability studies for public comment and these documents will be finalized soon in 2011 (8,9). Although the HC currently requires steady-state studies when accumulation is indicated for the drug, it is proposing to remove this requirement in its draft guidance (8). Replicate study designs can be conducted in US, EU and Canada. However, the HC allows other strategies such as add-on subjects and sequential designs; both strategies should be justified *a priori* and declared in the study protocol (8). Sequential designs have also been proposed by the FDA recently (10) and have already been included in the EMA guideline (4).

As shown in Table I, *in vivo* bioequivalence studies are usually conducted under fasting conditions, with the exception that FDA requires both fasting and fed studies for all orally administered immediate-release and modified-release drug products. However, fed studies are exempted by the FDA for immediate-release forms if the reference label (a) states that the product should be taken on an empty stomach, and/or (b) has no description about food effects on relative bioavailability or administration (7). In the EMA guideline, fed studies are needed if the reference label recommends intake only in fed state or when the reference product is a modified-release formulation (4). Otherwise, studies in fasting conditions are preferred as this is considered most sensitive to detect a potential difference between formulations. In the draft HC guidance, bioequivalence should be demonstrated under both fasted and fed conditions for critical dose drugs,

Table 1. A Comparison of Regulatory Requirements for Conduct of Bioequivalence Studies Using Pharmacokinetic Measures

Scope	FDA/US			EMA/EU		HC/Canada		WHO	
	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action	Oral products, systemic action
Study Design	Standard design ^a in general. Replicate designs and sequential designs are optional. Parallel designs when necessary.	Standard design ^a in general. Alternative designs such as parallel group designs (or in exceptional cases, steady state studies in healthy volunteers or patients) are acceptable when justified. Multiple-dose studies required for modified-release products.	Standard design ^a in general. Replicate designs, add-ons are optional. Parallel designs are sometimes necessary. Multiple-dose studies for modified release products required if significant accumulation at steady state. ^b						
Fasting or Fed Conditions	Fasting and fed studies for both immediate- and modified-release products. Fasting if reference label states that the product should be taken on an empty stomach or has no mention of food effect.	Fasting for most immediate-release products. Fed studies if reference label indicates intake only with food. Fasting and fed studies for some immediate-release products with specific formulation characteristics and all modified-release products.	Fasting for most immediate-release products. Fed studies if reference label indicates intake only with food. Fasting and fed studies for critical dose drugs and drugs with nonlinear pharmacokinetics. Fed or fasted study justified if there is significant safety risk from single-dose in the absence or presence of food.						
Meal Composition	High-fat and high-calorie	Follow reference SmPC. ^c If no such information, use high fat and high calorie meal. In case of modified-release products high fat and high calorie meal.	High-fat and high-calorie. Use of other meals should be justified <i>a priori</i> .						
Strength to be Tested	The highest strength. For safety concerns, a lower strength can be used.	One or two strengths, depending on proportionality in composition and linearity in pharmacokinetics. Use of the highest strength preferred, or in the case of nonlinear pharmacokinetics, strength that is judged to be most discriminative of formulation performance.	Same dose of each product should be used. May not require all strengths if there are similar proportions of excipients and dissolution characteristics. Highest strength preferred, or in the case of nonlinear pharmacokinetics, strength that is judged to be most discriminative of formulation performance.						

^a Standard design: single-dose, two-period, crossover study in healthy volunteers^b This requirement was proposed to be removed in the 2010 draft HC guidance^c SmPC, Summary of Product Characteristics

drugs exhibiting non-linear pharmacokinetics and drugs in modified-release dosage forms (including delayed-release formulations) (8). If, however, there is a documented serious safety risk to subjects from single-dose administration of the drug or drug product in either the absence or presence of food, an appropriately designed study conducted in the indicated condition of use (fed or fasted state) may be acceptable (8). The WHO guideline indicates that fed-state studies are needed when (a) the reference product is a modified release formulation, and/or (b) when the label of a reference product indicates that the drug product should be taken with food (1).

Regarding the strength to be tested, the FDA guidance only requires *in vivo* bioequivalence studies on the highest strength except when there may be a safety issue at the highest strength. However, additional bioequivalence studies are needed if the formulations are not proportionally similar (6). Although use of the highest strength is generally preferred, the EMA guideline and HC guidance indicated that one or two strengths may be needed, depending on the proportionality in composition and linearity in pharmacokinetics (4,9). In the case of drugs with nonlinear pharmacokinetics, the strength used for bioequivalence studies is the one judged to be most discriminative of formulation performance. For modified release formulations, the EMA guideline requires fasting study on each strength of single-unit formulations, but only on the highest strength of multiple-unit formulations if there is linear pharmacokinetics with multiple strengths (5). Also, food study is required on the same strength(s) as that (those) of the pivotal bioequivalence study (ies) (5). The HC currently requires steady-state studies on the highest strength for extended-release products that accumulate after multiple doses. However, the draft HC guidance has proposed to remove this requirement (8,9).

It is widely recognized that the parent drug is more sensitive to changes in formulation performance and thus measurement of only parent drug is recommended for bioequivalence determination. Use of metabolite(s) is not encouraged by the EMA even in the case of prodrugs, whereas the WHO guideline indicates that metabolite measurement is acceptable if the drug substance in the dosage form is a prodrug (1,4). In general, only under certain circumstances will metabolites be used for bioequivalence evaluation. For the EMA, these exceptional cases may include the following: (a) sensitivity of bioanalytical method is low for parent drug, (b) exposure of parent drug is reflected by exposure of metabolite(s), (c) metabolite formation is not saturated at the usual doses, and/or (d) a prodrug that has low plasma concentrations and is quickly eliminated (e.g., mycophenolate mofetil) (4). In the case of the FDA, only parent drug determination is needed for bioequivalence. However, both parent drug and metabolite are recommended if the metabolite is formed in the gut wall or from other pre-systemic metabolism and it contributes meaningfully to safety and/or efficacy (6). Overall, measurement of metabolite is preferred globally when parent drug levels are too low to allow reliable measurement (1,4,6,8).

Statistical analyses for pharmacokinetic studies are generally performed on logarithmically transformed AUC and $C_{\max}$ data. An average bioequivalence approach is recommended using a two one-sided tests procedure that involves

the computation of 90% confidence interval (CI) for the ratio of population geometric means of AUC or $C_{\max}$ between test and reference products (11). To establish bioequivalence, the calculated 90% CI should fall within 80–125% of the reference product. This is applicable to both AUC and $C_{\max}$ for most regulatory authorities with the exception of HC that applies 90% CI for AUC, but only requires point estimate for $C_{\max}$ (mean test/reference ratio) to be within 80–125% (9). Note that highly variable drug products and critical dose (or narrow therapeutic index) drugs have different bioequivalence criteria as will be discussed below. For the EMA, it is acceptable to use a two-stage approach for bioequivalence demonstration provided that stopping criteria are clearly defined *a priori* and appropriate measure is taken to preserve the overall type I error of the study (4). Similarly, the draft HC guidance proposes that the level of confidence for add-on study design be adjusted using Bonferroni procedure and *t*-value be that for $p=0.025$ instead of 0.05 (8).

Highly Variable Drug Products

Highly variable drug products are currently defined to have intra- (or within-) subject variability $\geq 30\%$. The requirement for highly variable drug products to meet the conventional bioequivalence criteria, i.e., 90% CI to be within 80–125% for $C_{\max}$ and AUC, may unnecessarily expose a large number of subjects to the drug. To reduce the sample size, one approach may be to perform *in vivo* bioequivalence studies using a replicate crossover design. Another approach is to widen the acceptance criteria for bioequivalence of these drug products. The EMA guideline indicates that the acceptance criteria for $C_{\max}$ of highly variable drug products can be widened to a maximum of 69.84–143.19% as long as widening of this parameter is considered clinically irrelevant with a sound clinical justification (4). The extent of widening is based on the within-subject variability of the reference product (assessed from replicate administration) using a scaled-average bioequivalence method. Furthermore, in these bioequivalence studies, the geometric mean ratio (test/reference) should be within 80–125% (4). Recently, the FDA has also adopted a similar approach for highly variable drug products (12–14). The FDA allows the use of a fully or partially replicated treatment design in which the reference product is given twice and the test product is given once or twice in a three-way or four-way crossover study design, respectively. Giving the reference product twice allows estimation of the within-subject variability of the reference product. In contrast, the draft HC guidance indicates that there is no compelling need for a distinct category of “highly variable” drug products since sufficient flexibility has been allowed in study design (such as add-ons and sequential designs) to address the underlying issue (9), and most of the time the criterion for $C_{\max}$ is the test/reference ratio rather than the CI limit in Canada.

Narrow Therapeutic Range/Index or Critical Dose Drugs

The FDA defines *narrow therapeutic range* drug products as those products containing certain potent drug substances that require pharmacokinetic (therapeutic drug concentration) or pharmacodynamic monitoring, and/or where product

labeling indicates a narrow therapeutic range designation (6). Examples of these drugs may include digoxin, lithium, phenytoin, theophylline, and warfarin (6). The FDA recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. However, the current FDA guidance indicates that the traditional bioequivalence limits (90% CI of 80–125%) remain unchanged for these drug products (6). Since narrow therapeutic range drugs often have low within-subject variability, a 20% fluctuation in plasma concentration may be clinically significant. In view of these concerns, the Office of Generic Drugs in the FDA is now investigating new approaches for establishing bioequivalence of these drug products. In contrast, the EMA guideline has stated that the 90% CI acceptance range for AUC should be tightened to 90.00–111.11% for *narrow therapeutic index* drug products. Moreover, the same criterion should be applicable to $C_{\max}$, where this parameter is of particular importance for safety, efficacy, or drug level monitoring (4). The EMA guideline acknowledges that it is not possible to define a set of criteria for categorizing drugs as narrow therapeutic index drugs and thus each drug product must be decided case by case based on clinical considerations (4). The draft HC guidance has specifically created a new category of *critical dose drugs* for those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death (9). The draft HC guidance has proposed to tighten the 90% CI of these drugs to be within 90.0–112.0% for AUC and 80.0–125% for $C_{\max}$, which is applicable to both fasting and fed studies (9).

Drugs with an Important Early Time of Onset

Bioequivalence can generally be demonstrated by measurements of peak and total exposure as expressed by $C_{\max}$ and AUC, respectively. Under certain circumstances, however, an early drug exposure may be needed to allow for an appropriate control of onset of pharmacodynamic effect and/or a more complete comparison of pharmacokinetic profiles. For example, the control of drug input may be important to ensure rapid onset of an analgesic effect or to avoid reflex tachycardia of an antihypertensive agent. In this regard, the FDA guidance has recommended the use of partial AUC as an early exposure measure for orally administered, immediate-release products on the basis of clinical efficacy/safety and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (6). In this context, the FDA guidance recommends that the partial area be truncated at the population median of $T_{\max}$ values for the reference formulation (6). The metric of partial AUCs is also recently proposed by the FDA for a multiphasic modified-release product (zolpidem tartrate extended-release) formulated to achieve rapid onset of action followed by sustained response (15). In this case, three consecutive segments of partial AUC are used for profile comparison, ensuring that the rate and extent of drug

availability are not significantly different between the test and reference products in all time intervals. The cutoffs for these partial AUC measures have been determined based on the results of pharmacokinetic/pharmacodynamic and clinical studies conducted for the reference product (16). Similarly, for drugs with an early time of onset or rapid rate of absorption that is considered important, the draft HC guidance indicates that the relative mean AUC_{Reftmax} ratio of the test to reference formulation should be within 80.0% to 125.0%, where AUC_{Reftmax} for a test product is defined as the area under the curve to the time of the maximum concentration of the reference product, calculated for each study subject (9).

Comparative Pharmacodynamic Studies and/or Comparative Clinical Trials

Bioequivalence based on pharmacokinetic endpoints suggests that equivalence in rate and extent of systemic exposure equates to similarity in clinical effectiveness and safety. While this assumption may be valid for most systemically absorbed drugs, similar systemic exposure may not indicate bioequivalence of locally acting drug products. For example, bioequivalence for drug products acting upon cutaneous structures may not be extrapolated from plasma concentrations because (a) dose applied topically is less defined, (b) plasma concentrations do not reflect concentrations at the site of action, and (c) topical formulation bioavailability is known to be affected by multiple factors, such as cutaneous attributes, solubility and concentration of active ingredient, characteristics of vehicles, and disease states. Hence, bioequivalence documentation of locally acting drug products is generally based on clinical endpoints or acute pharmacodynamic measures, e.g., vasoconstrictor assay for topical corticosteroids (17). The EMA published a note for guidance in 1995 on the clinical requirements for locally applied, locally acting products (18). Nevertheless, this note is rather obsolete now and its revision by the EMA is currently underway. In general, conventional bioequivalence limits are not acceptable in pivotal clinical equivalence studies for European submissions and typically a two-sided 95% CI is used for treatment differences. The HC has published three guidances for specific products that use pharmacodynamic and/or clinical endpoints for bioequivalence demonstration, which includes short-acting beta2-agonist metered dose inhalers (19), inhaled corticosteroids (20), and nasal steroids (21). In the US, there are also several guidances on bioequivalence of specific topical products (22). Typically, a randomized, double-blind, placebo-controlled, parallel group study is required (placebos are not needed for drugs treating infectious diseases). Bioequivalence is established if the test product is equivalent to the reference product and superior to the placebo treatment. To establish bioequivalence using pharmacodynamic and/or clinical endpoints, the 90% CI of the test-reference difference should be contained within $[-0.20, +0.20]$. For many drugs, proof that the dose(s) studied for equivalence is situated in the discriminative part of the dose–response curve may avoid the study of a larger dose of the reference product (23). This may also enable the use of a dose-scale approach where bioequivalence is determined based on the projected equivalent dose of the test product

and not simply on the pharmacodynamic/efficacy endpoint on the dose–response curve where the non-linear relationship will often bias the bioequivalence comparison negatively or positively (if too close to the $E_{\max}$). The dose-scale approach has been used by the FDA to set the bioequivalence limit for albuterol metered dose inhalers (24).

Since systemic exposure of locally acting drug products may entail a risk of systemic adverse reactions, an additional comparative pharmacokinetic study is required globally to ensure that systemic drug exposure for the test product is similar to the reference product, e.g., tretinoin topical formulation. The conventional bioequivalence limits of 80–125% (90% CI) can be applied to these pharmacokinetic studies. However, the EMA guideline only requires that the upper limit of 90% CI does not exceed 125.00% for these studies (4).

IN VITRO BIOEQUIVALENCE TESTING

Comparative *in vitro* studies may serve as a surrogate for *in vivo* bioequivalence studies under certain circumstances. For example, it is not always necessary to perform *in vivo* bioequivalence studies on a drug product that is marketed with several different dose strengths. Bioequivalence studies are performed on the highest dose strength and the sponsor may request a biowaiver for the lower strength drug products. In this case, the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength (usually the highest strength) on which bioequivalence testing has been conducted, an *in vivo* bioequivalence demonstration of one or more lower strengths can be waived based on *in vitro* dissolution (6). When used for biowaiver for lower strength (s) of the product, *in vitro* dissolution profile for the highest strength and lower strength(s) are compared using f_2 similarity test (6).

In conjunction with BCS, comparative *in vitro* dissolution testing has also been employed to waive *in vivo* bioequivalence studies for certain drugs in immediate-release solid oral dosage forms (1,3,4,6). When used for equivalence demonstration, the *in vitro* dissolution test must include dissolution profile comparisons between the multisource (generic) product and comparator (reference) product in three dissolution media: pH 1.2, 4.5 and 6.8. The BCS-based biowaiver approach has been used by the FDA, EMA and WHO except for the HC. However, this approach is currently under discussion in Canada. It is noteworthy that the BCS-based biowaivers are not applicable to narrow therapeutic index/range drugs or drugs designed to be absorbed in the oral cavity (e.g., sublingual or buccal tablets) (1,3,4).

Regulatory requirements for the BCS-based biowaivers vary among countries and/or regions. For example, the FDA only waives the requirement of *in vivo* bioequivalence studies for BCS Class 1 (highly soluble, highly permeable) drugs that are formulated in very rapidly dissolving ($\geq 85\%$ in 15 min) or rapidly dissolving ($\geq 85\%$ in 30 min) products (3). In contrast, in addition to BCS Class 1 drugs, the EMA guideline now proposes biowaivers for BCS Class 3 drugs with high solubility and limited absorption provided that both test and reference products have very rapid ($\geq 85\%$ in 15 min) *in vitro* dissolution characteristics (4). The WHO proposal for the

BCS-based biowaivers is similar to that from the EMA for BCS Class 1 and 3 drugs, with an additional biowaiver for BCS Class 2 weak acids if (a) API has a dose/solubility ratio of 250 ml or less at pH 6.8, (b) multisource product is rapidly dissolving ($\geq 85\%$ in 30 min in pH 6.8), and (c) dissolution profile is similar to that of comparator product at pH 1.2, 4.5 and 6.8 under defined dissolution conditions (1).

REFERENCE OR COMPARATOR PRODUCTS

The design of a bioequivalence study must include a reference (or comparator) product for comparison purpose. In the US, an RLD is identified by the FDA as the drug product upon which a generic applicant relies in seeking approval of its abbreviated new drug application (ANDA). The RLD is usually the drug product initially manufactured by the innovator (brand) drug company that contains a complete new drug application. The RLD is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) (25). By designating a single RLD as the standard to which all generic versions must be shown to be equivalent, the FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. The selection of reference products in Europe is more complicated due to the existence of several national markets. The EMA guideline indicates that for Article 10(1) and 10(3) marketing authorization applications, reference must be made to the dossier of a reference medicinal product for which a marketing authorization is or has been granted on the basis of a complete dossier (4). The choice of the reference medicinal product for which bioequivalence has been demonstrated by appropriate bioavailability studies should be justified by the sponsor (4). Yet, for abridged applications to numerous member states in Europe, the study of a reference product from one state is sufficient (as long as it can be justified — normally supported by comparative dissolution data — that the reference product used in the study is comparable to the national reference product). The Canadian reference product used in bioequivalence studies is usually the product approved in Canada (8). However, the HC allows for the use of a reference product from another country as long as the sponsor provides evidence to show that the product chosen is the same as the one sold on the Canadian market, in that it has the same visual characteristics and similar *in vitro* characteristics, and that the product has simple drug kinetics and formulation (8). The HC has more flexible regulation than the FDA and EMA in this regard.

The WHO considers a comparator product as (a) the product with which a generic product is expected to be interchangeable in clinical practice, (b) the product whose safety and efficacy data have been basis for marketing approval and will be basis for approval of all its pharmaceutical equivalents, and (c) the product that generally has the largest market share (1). As such, a comparator product is usually the original or innovator product. However, it is challenging to select an appropriate comparator product when (a) there is no global agreement on the selection of reference products, (b) national market leaders may be more relevant for patient safety, (c) market leaders may not be the originator product, (d) market leaders may differ from country to country, or (e) originators may differ in different

countries. In view of these concerns, the WHO has suggested the following scheme (in order of preference) for national regulatory authorities to choose a comparator product: (i) nationally authorized innovator, (ii) the WHO comparator product, (iii) ICH *et al.* innovator, and (iv) well-selected comparator (1).

CHALLENGES IN CONDUCTING *IN VIVO* BIOEQUIVALENCE STUDIES FOR THE GLOBAL MARKET

The demonstration of *in vivo* bioequivalence is the most expensive part of generic drug development program that also comes with the most risk of failure. The generic drug manufacturer may decide not to develop the proposed multisource product due to the failure of a bioequivalence study, the cost of reformulation and/or the performance of another new bioequivalence study. Moreover, the delay in time for submitting the generic drug application to regulatory authorities may preclude further development due to the loss of competitive advantages. The most significant problem is the comparability of reference products with full clinical documentation. In most cases, identical reference products with same clinical documentation are not available on all national markets globally and consequently, regulatory authorities may require studies conducted with their national reference products.

Moreover, there are additional multiple challenges in conducting *in vivo* bioequivalence studies for the global market. Regulatory challenges in harmonization may include burdens on inspection for these studies conducted in foreign sites and language barrier to access publicly available information on study requirements. The quality and conduct of these human studies may vary with the level of experience. A potential challenge in performing bioequivalence studies is the differences in the diet constituents from various countries

that may affect the relative bioavailability of some drugs. The use of vulnerable populations for bioequivalence studies in underdeveloped countries is an ethical concern. Recruitment of female volunteers for *in vivo* bioequivalence studies is challenging in certain countries. Other logistical challenges may be related to the timeline for starting bioequivalence studies in different jurisdictions, issues with travel requirements for monitoring these studies and/or shipping of investigational drug products and plasma samples.

HARMONIZATION OF REGULATORY REQUIREMENTS

The increased globalization of pharmaceutical industry has triggered the need for harmonization of scientific and regulatory requirements for marketing of safe, effective and therapeutically equivalent multisource drug products. However, differing regulatory approaches and differing levels of commitment in resources continue to create formidable barriers to harmonization. Currently, there seems to be an increasing trend of individual countries requiring separate bioequivalence studies for regulatory approval of generic products, e.g., using domestic reference products or conducting studies at certified centers in their respective countries. Examples of major challenges to global harmonization of regulatory standards, including some that were not discussed at this workshop, are listed in Table II. An international platform for harmonization of these regulatory requirements is needed to move the process forward. The International Conference on Harmonization (ICH), including US, EU and Japan, has held multiple meetings over the past 20 years and had significant progress on a number of regulatory issues. The focus of ICH has been to harmonize the registration submissions for new drug applications and has not addressed generic or multisource drug products. On the other hand, the WHO has made progress on “non-regulated” geographic

Table II. Challenges to Harmonization of Regulatory Requirements for Therapeutic Equivalence of Multisource Drug Products

Requirements	Challenge	Comments/Examples
Bioanalytical methods	Validation	
<i>In vitro</i> requirements	Pharmaceutical equivalence	Definition (e.g., capsule versus tablet)
	Comparative drug release/dissolution profiles	Use of similarity test to replace <i>in vivo</i> bioequivalence studies
	BCS	Extension of BCS-based biowaivers
<i>In vivo</i> requirements	Chemistry, manufacturing and controls	Different requirements (e.g., stability)
	Reference drug product	Reference product is not the same in each domestic marketplace; selection of the dose strength for bioequivalence study is not harmonized
	Design of bioequivalence studies	Special designs for highly variable drug products, long half-life drugs, etc.
	Subject population	Different subject populations and different diets
	Food effect and sprinkle studies	Different requirements globally
	Acceptance criteria for bioequivalence studies	Different criteria for highly variable drug products, critical dose drugs, etc.
Regulatory issues	Global conference on harmonization	An international platform for discussion such as ICH, WHO, and others is needed to begin harmonization process
	Regulatory inspection	Foreign inspection and sharing of inspection reports are not harmonized
	Contract research organization (CRO)	Certification of CRO, differences in quality

areas. In the context of quality standards for drug products, the ICH and Pharmacopeia Discussion Group have made tremendous advances in standardizing testing methods for both dissolution and stability.

It is unclear as to which international organization would be most appropriate to address harmonization issues on therapeutic equivalence of multisource drug products. As was done with the ICH, various aspects of harmonization could be addressed (Table II). Several of these issues may be resolved easily and certain issues are more challenging (such as the selection of a reference product). All scientists from academia, regulatory authorities and pharmaceutical industry are urged to contribute towards achieving consensus on globally acceptable bioequivalence criteria.

CONCLUSIONS

The scientific presentations and discussions at this workshop clearly indicated the need for harmonization of regulatory requirements on therapeutic equivalence of multisource drug products. From the past history, the ICH may not be interested in the process of harmonizing therapeutic equivalence regulations, and thus other routes should be vigorously explored. A small group of interested scientists along with regulators may meet and start identifying the areas where resolution can be achieved. It is possible to harmonize the testing methods or procedures even if the acceptance criteria cannot be harmonized. At least, three areas of harmonization can be easily explored: (a) bioanalytical methods, (b) *in vitro* studies including biowaiver based on BCS, and (c) *in vivo* bioequivalence studies. These topics can be discussed one by one. It is realized that harmonization should come from regulators and regulating agencies. However, scientists from academia and industry who are well familiar with the topics can work together with the regulators to help resolve the underlying issues. Institutions such as AAPS, EUFAPS, and/or FIP may provide neutral platform to discuss these areas.

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