Review Article

Theme: Human and Veterinary Therapeutics: Interspecies Extrapolations and Shared Challenges
Guest Editor: Marilyn Martinez

International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences

Barbara Davit,^{1,3} April C. Braddy,² Dale P. Conner,² and Lawrence X. Yu²

Received 29 November 2012; accepted 23 May 2013; published online 3 July 2013

Abstract. The objective of this article is to discuss the similarities and differences among bioequivalence approaches used by international regulatory authorities when reviewing applications for marketing new generic drug products which are systemically active and intended for oral administration. We focused on the 13 jurisdictions and organizations participating in the International Generic Drug Regulators Pilot. These are Australia, Brazil, Canada, China, Chinese Taipei, the European Medicines Association, Japan, Mexico, Singapore, South Korea, Switzerland, the USA, and the World Health Organization. We began with a comparison of how the various jurisdictions and organizations define a generic product and its corresponding reference product. We then compared the following bioequivalence approaches: recommended bioequivalence study designs, method of pharmacokinetic calculations and bioequivalence acceptance limits, recommendations for modifying bioequivalence study designs and limits for highly variable drugs and narrow therapeutic index drugs, provisions for waiving bioequivalence study requirements (granting biowaivers), and implementation of the Biopharmaceutics Classification System. We observed that, overall, there are more similarities than differences in bioequivalence approaches among the regulatory authorities surveyed.

KEY WORDS: bioequivalence; biopharmaceutics classification system; biowaivers; generic drugs; regulatory authority.

INTRODUCTION

Generic drugs are important options that allow greater access to health care. Generic drugs are copies of innovator (reference) drugs and are the same as those innovator drugs with respect to safety, strength, route of administration, quality, performance characteristics, and intended use (1). Throughout the world, an application for marketing approval of a new generic product must reference a corresponding product, which was approved on the basis of clinical trials to support claims of safety and efficacy. Various countries throughout the world, as well as organizations such as the Association of Southeast Asian Nations (ASEAN), European Union, and World Health Organization (WHO), have their own individual regulatory authorities and regulatory guidance for marketing approval of generic drug products (2). Within a jurisdiction, generic drugs are generally multisource drug products, defined as products marketed by more than one manufacturer and containing the same active pharmaceutical ingredient in the same dosage form intended to be administered by the same route of administration (3). Drug products

that contain the same active ingredient(s) have the same dosage form and route of administration and are identical in strength or concentration are designated pharmaceutical equivalents (4). Drug products that contain the same therapeutic moiety, but which are different salts, esters, or complexes of that moiety, are designated as pharmaceutical alternatives.

The establishment of bioequivalence (BE) is fundamental in successful applications for generic drug products (5). BE is established in order to demonstrate therapeutic equivalence between the generic (test) drug product and corresponding reference drug product. Therapeutically equivalent drug products can be substituted with the full expectation that the substituted (generic or test) product will produce the same safety effect and safety profile as the originally prescribed (reference) product. Establishment of BE allows bridging of preclinical and clinical data associated with the reference product to the generic product.

Bioavailability (BA) is defined as the rate and extent to which an active ingredient or active moiety is absorbed and becomes available at the site of action. BE drug products are pharmaceutical equivalents or pharmaceutical alternatives that display comparable bioavailability when studied under similar experimental conditions. Two products are considered bioequivalent when the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions (6).

¹ Merck Pharmaceuticals, Rahway, New Jersey, USA.

² Office of Generic Drugs, Center for Drug Evaluation and Research, US-FDA, Rockville, Maryland, USA.

³ To whom correspondence should be addressed. (e-mail: barbara.davit@merck.com)

Drug rate and extent of absorption are typically assessed by conducting *in vivo* studies in human subjects in which generic and reference drug plasma pharmacokinetic (PK) profiles are characterized and compared. As per the different regulatory authorities, BE can be established by PK, pharmacodynamic, clinical, or *in vitro* endpoint studies, in general descending order of preference (7). Pharmacodynamic, clinical, and/or *in vitro* endpoint studies are generally used for locally active drugs for which PK studies may not be adequate to establish BE (8). Although “*in vitro*” is ranked below “clinical” in FDA’s regulations, there are situations in which an *in vitro* approach is equally (or more) sensitive, accurate, and reproducible than conducting an *in vivo* study with clinical endpoints for establishing BE between two products (9). Finally, for generic products for which BE to the corresponding reference products is self-evident, a regulatory agency may waive the requirement for conducting a BE study (10). This is commonly referred to as granting a “biowaiver.”

Since most generic drug marketing applications are for drugs intended to be systemically available, this review will emphasize comparisons of regulatory considerations governing BE studies with PK endpoints. In a BE study with PK endpoints, the PK data are used to obtain peak drug plasma concentration ($C_{\max}$) as the BE measure of rate of absorption and area under the drug plasma concentration versus time profile [area under curve (AUC)] as the BE measure of extent of absorption. The time to peak drug plasma concentration, $T_{\max}$, is also an indicator of drug rate of absorption. It is a common practice to log-transform generic and reference AUC and $C_{\max}$ values and compare the geometric mean ratios (GMRs). Two products are deemed bioequivalent if these generic/reference GMRs fall within specified BE limits.

The BA/BE concept is pivotal to generic drug development throughout the world. Currently available approaches to determine BE of generic products are largely standardized, although there are still differences that can potentially lead to barriers in international data exchange. The objective of the following article is to survey international approaches for demonstrating BE of generic drug products, with an emphasis on ways in which the approaches are similar versus ways in which the approaches differ. Identification of such similarities and differences is a preliminary step for exploring ways to promote collaboration and convergence among regulatory health authorities who are faced with making decisions about the BE of generic drugs relative to corresponding reference products.

It is important to note that BE documentation has a pivotal role in new drug development as well. BE studies are used to establish links among (1) early and late clinical efficacy trial formulations, (2) formulations used in clinical trial and stability studies, if different, and (3) clinical trial formulations and to-be-marketed formulations (11). BE studies may be necessary to support some types of post-approval manufacturing, site, or formulation changes. Although the focus of this article is on generic drug development, all of the approaches discussed herein also apply to BE studies in the context of new drug development.

METHODS

The objective of this review is to compare across various international jurisdictions and organizations the regulatory

approaches for establishing BE of generic drugs to their corresponding reference drugs. The jurisdictions and organizations to be discussed will be those currently participating in the International Generic Drug Regulators Pilot (12,13). Table I lists the international jurisdictions and organizations to be discussed in this review, along with their corresponding regulatory agencies.

We compared similarities and differences in BE approaches for the following:

- Definitions of a generic and reference product
- Study design
- PK parameter calculations and BE acceptance limits
- Highly variable (HV) drugs
- Narrow therapeutic index (NTI) drugs and critical dose drugs
- Situations in which biowaivers are granted
- Use of the Biopharmaceutics Classification System (BCS) for granting biowaivers.

Sources of information were the BE guidelines published by the various regulatory agencies. Table I also lists the guidelines for *in vivo* BE and *in vitro* dissolution testing associated with each regulatory agency. Except where noted throughout this review, for BE study design, Australia and Switzerland follow the guidelines published by the European Medicines Agency (EMA), and Singapore follows the guidelines published by the ASEAN.

RESULTS

Definitions of a Generic Drug Product and Reference Drug Product

Table II shows how the different jurisdictions and organizations define a generic drug product. Australia, Brazil, Chinese Taipei, Japan, Switzerland, and the USA stipulate that a generic drug product must be pharmaceutically equivalent to the corresponding reference drug product. The above jurisdictions define pharmaceutical equivalents as containing identical amounts of the same active drug substance in the same dosage form and route of administration (4). Canada defines pharmaceutical equivalents as comparable dosage forms instead of as the same dosage form. Specifically, Section C.08.001.1 of the Canadian Food and Drug Regulations states that pharmaceutical equivalent means “a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients.” This means that, for example, a generic tablet could be compared to a reference that is a capsule.

In China, Singapore, and the ASEAN, generic drugs can be pharmaceutical alternatives to the reference drug product. Pharmaceutical alternatives must be of the same strength and route of administration; an example of suitable pharmaceutical alternatives is a capsule and a tablet containing the same active drug substance in the same strength. Similarly, South Korea and the WHO define a generic drug product as a pharmaceutical product that is interchangeable with the innovator. In the EMA, a generic should contain the same active substance and be in the same dosage form as the

Table I. Regulatory Authorities and Bioequivalence (BE) Guidelines of Various Jurisdictions and Organizations Participating in the International Generic Drugs Regulators Pilot (IGDRP)

Jurisdiction or organization	Agency	BE guideline(s) referenced	Date posted
Australia	Therapeutic Goods Administration (TGA)	Follows the European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence, with annotations (14)	January 2012
		Where noted, refer to the Australian Regulatory Guidelines for Prescription Medicines. Appendix 15: Biopharmaceutics Studies	June 2004
Brazil	National Agency of Sanitary Monitoring (Anvisa)	Guide for Relative Bioavailability/Bioequivalence Tests of Medicines (15)	May 2003
Canada	Health Canada (HC)	Comparative Bioavailability Standards: Formulations Used for Systemic Effects	May 2012
		Conduct and Analysis of Comparative Bioavailability Studies	May 2012
		Biopharmaceutics Classification System Biowaiver (Draft)	August 2012
China	State Food and Drug Administration (SFDA)	Bioavailability and Bioequivalence Studies for Chemical Drug Products	March 2005
Chinese Taipei	Taiwan (Chinese Taipei) Food and Drug Administration (TFDA)	Guideline on Bioavailability/Bioequivalence Studies (16)	April 2009
European Union (EU)	European Medicines Agency (EMA)	Guideline on the Investigation of Bioequivalence	January 2010
		Note for Guidance on Modified-Release Oral and Transdermal Dosage Forms	July 1999
Japan	Ministry of Health, Labour and Welfare (MHLW) Pharmaceuticals and Medical Devices Agency (PMDA)	Guideline for Bioequivalence Studies of Generic Products	February 2012
Mexico	The Federal Commission for the Protection Against Sanitary Risk (COFEPRIS)	Guidelines for Submission of Research Protocols to Demonstrate the Drug Interchangeability (17)	November 2012
		Guidelines for the Implementation of the Standard Nom-177-SSA1-1998 Establishing Tests and Procedures for Demonstrating that a Product is Interchangeable (18)	October 2012
Singapore	Health Sciences Authority (HSA)	Follows the Association of Southeast Asian Nations (ASEAN) Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (19)	July 2004
South Korea	Korea Food and Drug Administration (KFDA)	Guidance Document for Bioequivalence Study	December 2008
Switzerland	Swiss Agency for Therapeutic Products (Swissmedic)	Follows the EMA Guideline on the Investigation of Bioequivalence, with annotations (20)	January 2010
		Where noted, refer to Swissmedic Administrative Ordinance Instructions: Application and Authorisation for Generics	October 2012
United Nations (UN)	World Health Organization (WHO)	Multisource Generic Pharmaceutical Products: Guideline on Registration Requirements to Establish Interchangeability (Draft Revision)	October 2005
		General Notes on Biopharmaceutic Classification System (BCS)-Based Biowaiver Applications	November 2011
United States of America (USA)	US Food and Drug Administration (USFDA)	Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations	March 2003
		Food-Effect Bioavailability and Fed Bioequivalence Studies	January 2003
		Waivers of <i>In Vivo</i> Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System	August 2000
		Bioequivalence Recommendations for Specific Products	June 2010

reference product. “Same active substance” is defined as a different salt, ester, ether, isomer, mixture of isomers, complexes, or derivatives of an active substance, unless differing significantly in properties of safety and efficacy. All jurisdictions emphasize that the approved generic drug product must meet quality specifications set by the regulatory agency granting the approval.

Table II also shows how the different jurisdictions and organizations define a suitable reference drug product. In general, the reference or innovator drug product must be

approved and in the jurisdiction in which the generic drug applicant seeks marketing authorization. Generally, the preferred reference product is the one sold domestically, although only Brazil formally states this as an additional requirement. In Australia, Canada, and Switzerland, it is possible in limited situations to use a reference product, which is approved and marketed outside of the country, provided that certain rigorous criteria are met. Mexico formerly required pharmaceutical manufacturers to have production facilities in the country (36). In 2008, the Mexican government abolished the legislation

Table II. Test and Reference Product Information, Describing What Type of Formulation can be Marketed as a Generic Drug Product, and What Is the Appropriate Reference Product

Jurisdiction or organization	Generic drug product	Definitions	Reference/innovator drug product
Australia	The proposed generic drug product must be a pharmaceutical equivalent of the reference product (21)		The TGA prefers that the proposed generic product reference a leading brand product purchased within Australia. When justified by appropriate <i>in vitro</i> comparative studies, the TGA will accept BE studies where the innovator drug product was sourced from outside of Australia, although this approach is not permitted for certain types of drug substances, such as NTI drugs, drugs with complex or nonlinear kinetics, and HV drugs(14,22) The reference product must be registered at ANVISA, supported by documentation related to its safety, efficacy, and quality, and it must be sold in the Brazilian market
Brazil	A drug product that contains the same active drug substance, same pharmaceutical dosage form, same route of administration, dosing, and therapeutic indication as the reference product (23)		
Canada	The proposed generic drug product must be a pharmaceutical equivalent of the reference product (24)		(A) A drug product in respect of which a notice of compliance is issued in pursuant with Canadian regulations and which is marketed in Canada by the innovator of the drug (B) A drug product, acceptable to the Minister (of Health), that can be used for the purposes of demonstrating BE on the basis of pharmaceutical and. Where applicable, bioavailability characteristic, where a drug in respect of which a notice of compliance has been issued in pursuant with the Canadian regulations cannot be used for that purpose because it is no longer marketed in Canada (C) A drug product, that is acceptable to the Minister (of Health) that can be used for the purpose of demonstrating bioequivalence on the basis of the pharmaceutical and. Where applicable, bioavailability, characteristics, in comparison to a drug referred according to their regulations (25) The corresponding innovator's drug product or the major market corresponding drug product
China	Essentially similar products, defined as either pharmaceutical equivalents or pharmaceutical alternatives (26)		
Chinese Taipei	A product that contains the same active ingredient(s) and is comparable to an approved innovator's medicinal product in dosage form, strength, route of administration, quality characteristics, and intended use (27)		Generally the innovator drug product marketed in Chinese Taipei, or the first approval drug product in Chinese Taipei
EMA	A drug product that has the same qualitatively (Q1) and quantitatively (Q2) composition in active substances, having the same pharmaceutical form as the reference product Different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties in regards to safety and/or efficacy (3)		A drug product whose marketing authorization in the EU has been granted on the basis of a complete dossier If there are several dosage forms of this medicinal product on the market, the reference should be the dosage form used for the initial approval of the concerned medicinal product and which was used in the clinical efficacy and safety studies (if available) A drug product that has been approved as a new drug, or a drug that corresponds to one (29).
Japan	The proposed generic product must be a pharmaceutical equivalent of the reference product (28).		
Mexico	The formulation must be pharmaceutically equivalent to that of the reference product (30)		A drug product that was registered with the Ministry of Health, which is available commercially and that is selected pursuant to the criteria established in the official regulations (31)
Singapore / ASEAN	Essentially similar products, defined as either pharmaceutical equivalents or pharmaceutical alternatives (32)		An innovator drug product, which is a drug product that is authorized and marketed on the basis of a full dossier, i.e., including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data
South Korea	A drug product whose active ingredient and route of administration is the same as those of the reference product (33)		A drug that is approved (or an approved imported drug product) the safety and efficacy of which has been established or recognized by the Commissioner of the Korea FDA
Switzerland	A substitutable generic drug formulation must be pharmaceutically equivalent to that of the reference product (20) Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties in regards to safety and/or efficacy The formulation must be pharmaceutically equivalent to that of the reference product (4)		The original product which is authorized in Switzerland, or A product registered outside of Switzerland, provided that it meets criteria for proving comparability to the original Swiss product (34)
USA			A reference listed drug means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA
WHO	A pharmaceutical product that is interchangeable with the innovator, which is usually marketed with license from the innovator company and marketed after expiry of the patent or other exclusivity rights (35)		A drug product that is usually the first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization)

requiring companies to have a plant in Mexico if they wished to distribute their products (37).

The WHO Prequalification of Medicines Programme (PQP) defines the reference product as one that is usually the first authorized for marketing, normally a patented product, on the basis of documentation of safety, efficacy, and quality, as per the requirements in effect at the time of authorization. The PQP places further stipulations on what would be considered an acceptable reference product. The primary stipulation is that comparator products should be purchased from a well-regulated market with stringent regulatory authority, that is, from countries participating in the International Conference on Harmonization. This is an important point because unlike national regulatory agencies, the WHO is not tied to any specific national market, and the use of an innovative product from “anywhere” as a reference could be problematic.

General BE Study Design

All require that a proposed generic drug product demonstrate that it is bioequivalent to the corresponding reference product. Table III shows similarities and differences in BE study design recommendations across these jurisdictions and organizations. Most often, the recommended BE study design is a randomized, single-dose, two-way crossover in healthy normal subjects. Patients should be used for reasons of safety only. Japan recommends using achlorhydric subjects in BE studies in some cases. Most of the jurisdictions and organizations recommend that a BE study enroll at least 12 subjects; a few suggest 18 or 24. With respect to subject demographics, all recommend age range and body weight restrictions. Most recommend that both male and female subjects be enrolled.

All recommend that generally the highest dose strength be used for *in vivo* BE studies, unless reasons of safety justify using a lower strength. In the case of drug substances that are characterized by nonlinear PK over the clinical dosing range, Canada, the EMA, USA, and WHO specify which dose strength should be used in these cases, depending on the type of nonlinearity and the underlying mechanism. All ask that the parent drug be measured in the appropriate biological fluid and subjected to BE statistics, unless the parent cannot be measured accurately and reproducibly. This is the case even for prodrugs. However, the jurisdictions and organizations differ in recommending other situations where it is necessary to measure metabolites in a BE study and what type of statistical evaluation should be performed on such metabolites. There is very little common ground regarding the metabolite measurement issue.

Australia, Canada, the EMA, and USA will accept a two-stage group-sequential BE study design in limited circumstances, provided that (1) a desirable overall type I error rate is maintained and (2) the analysis of the first stage is treated as an interim analysis and both analyses are conducted at adjusted significance levels. In addition, Canada and the USA will accept a two-stage adaptive BE study design, and Japan and South Korea will accept add-on studies. All state that the proposal and specifics of using a group-sequential, adaptive, or add-on study must be specified *a priori* in the study protocol.

BE Study Design Types Recommended for Various Solid Dosage Forms

Table IV shows similarities and differences in BE study type for various dosage forms. All jurisdictions and organizations request at least a single-dose, fasting BE study for immediate-release (IR) solid oral dosage forms. The USA is the only jurisdiction that requests a single-dose fed BE study routinely for IR oral products, with few exceptions (45). Brazil, Canada, the EMA, and Singapore/ASEAN request a fed BE study for IR oral products under certain circumstances. All request that a fed BE study be conducted for modified-release (MR) oral dosage forms. Most emphasize that the drug product should be given no later than 30 min following meal consumption. Some specify meal composition in their respective BE guidelines. Canada, the EMA, Chinese Taipei, South Korea, and the USA (46) recommend that, in the fed BE study, the drug product be administered with a high-fat meal that is high in kilocalories. The WHO recommends that the meal be based on local custom and diet.

At present, only two jurisdictions provide guidance on whether BE should be established for alternative modes of administration for MR oral formulations, specifically for sprinkling on soft food. These are Canada and the USA. Canada recommends that the applicant contact Health Canada prior to commencement to verify the most appropriate mode of drug administration prior to the biostudy (25). Data should be provided to demonstrate that the technology used in the formulation is robust and that the controlled-release properties, if any, are not altered during the proposed period of time by exposure to the foods specified in the labeling. The USA recommends that, when the labeling for the RLD for a MR drug product indicates that the product may be sprinkled on soft foods, an *in vivo* sprinkle BE study comparing the test and RLD products should be performed (47). Both products should be sprinkled on one of the soft foods listed in the labeling (e.g., applesauce). The BE data should be analyzed using the average BE approach; acceptance criteria are that the 90% confidence intervals (CIs) of the test/reference GMRs for AUC and C_{max} should fall within 80–125% limits.

The jurisdictions and organizations request multiple-dose BE studies under varying circumstances. All recommend that this study design may be necessary when the BE study must be conducted in patients for which the drug product is indicated, for safety reasons. China, Chinese Taipei, the EMA, South Korea, and the WHO recommend multiple-dose BE studies in some or all circumstances (depending on the jurisdiction/organization) for MR oral drug products. The EMA publishes a guideline on developing generic transdermal dosage forms, and requests both single- and multiple-dose BE studies for generic versions of these formulations (48). Brazil, Japan, and the WHO organization recommend that multiple-dose BE studies be used when drug PK is highly variable or where assay sensitivity is too low to accurately characterize a PK profile following single dose administration. Chinese Taipei, Singapore/ASAEN, and the WHO also recommend use of multiple-dose BE studies for drugs that exhibit nonlinear PK.

Calculating PK Parameters and BE Statistics

Table V presents similarities and differences in determining PK parameters and BE statistics. The basic PK

Table III. Similarities and Differences in General BE Study Design

Number of units of test product to be manufactured for the bioequivalence study	
Similarities	Most specify a minimum test product batch size
Differences	Australia, Canada, Chinese Taipei, EMA, USA, Switzerland, WHO: a minimum of 10% of the commercial batch size or 100,000 units, whichever is greater Brazil, Singapore/ASEAN: Not specified China: a scaled-up batch or a full production batch Japan: It is recommended to use a lot manufactured at the same lot size as the full-scale production. However, a lot manufactured at a scale of not less than 1/10 of a full-scale production also can be used. South Korea: At least 100,000 units
Basic study design	
Similarities	All recommend the following BE study designs The standard study design is a two-period crossover, in which each subject is given the test and reference formulations; Replicated crossover designs may also be used; and Parallel designs may be used for long half-life drugs
Differences	None in this regard
Subjects	
Similarities	All request healthy normal subjects, unless, for reasons of safety, it becomes necessary to use patients
Differences	Japan: subjects with low gastric acidity (achlorhydric subjects) should be employed in cases where (1) the use of the drug is not limited to a specific population; and (2) the test and reference products show a significant difference in (<i>in vitro</i>) dissolution at around pH 6.8, or between pH 3.0–6.8 for basic drugs. This rule is not applied to enteric-coated products
Age range	
Similarities	All specify that studies should be conducted in adults
Differences	Brazil: 18–50 Canada, Mexico, Singapore/ASEAN, WHO: 18–55 China: 18–40 Chinese Taipei, Japan: Healthy adults EMA, USA: At least 18 years of age South Korea: 19–55 USA: At least 18 years of age, and; if the drug product is to be used primarily in the elderly, the study should include as many subjects as possible of 60 years of age or older
Body weight restrictions	
Similarities	All specify a body weight range, with variations listed below
Differences	Brazil: body weight should be $\pm 15\%$ of the weight considered normal for men and women, taking into account height and physical structure Canada, EMA, Singapore/ASEAN: Body Mass Index (BMI) within 18.5 and 30 kg/m ² China: within the normal range according to accepted normal values for BMI; avoid high variances in subjects' body weights Chinese Taipei: consideration of demographic attributes of a healthy normal adult population Japan: Not specified Mexico: body weight should be no different than $\pm 10\%$ of the weight South Korea: a medical doctor should consider the age and health condition of the subjects USA: individuals representative of the general population WHO: weight within an acceptable range according to accepted life tables
Gender, ethnicity	
Similarities	Any females used in the bioequivalence studies should not be pregnant
Differences	Brazil: depending on the drug product, the same number of males and females, to be distributed equally between the sequences China: in general, it is recommended to recruit healthy male subjects. The study population should be determined based on the specific situation for each drug product; if female subjects are recruited they should not be pregnant EMA, Canada, Chinese Taipei, Singapore/ASEAN, South Korea, USA, WHO: Subjects can belong to either sex Japan: no mention other than healthy adult subjects Mexico: use subjects of one sex to avoid gender-related pharmacokinetic differences
Number of subjects	
Similarities	All request a minimum of 12 subjects, with the exception of the jurisdictions listed below
Differences	China: 18–24 Japan: a sufficient number to show BE Mexico: 24 unless scientifically justified
Genotyping or phenotyping	
Similarities	All either (1) do not mention; or (2) recommend for safety or pharmacokinetic reasons
Differences	Brazil, Canada, Japan, Mexico, South Korea, USA: Not mentioned China, EMA, Singapore/ASEAN, WHO: Consider for safety or pharmacokinetic reasons
Dose strength used in the <i>in vivo</i> studies	
Similarities	All recommend that generally <i>in vivo</i> studies should be performed on the highest strength, unless reasons of safety justify use of a lower strength
Differences	Some jurisdictions specify which strength should be used for drugs with nonlinear PK over the clinical dosing range, as follows Australia: imposes the following restrictions on BE studies of generic drugs with non-linear or complex PK Only a drug product marketed in Australia is acceptable as the reference

Table III. (continued)

Once this criterion is met, follow the recommendations in the EMA Guidelines	
Canada, EMA: the strength to be used depends upon the type of nonlinearity and the underlying causes	
If the nonlinearity is characterized by greater than proportional increases in AUC with increasing dose, conduct the BE studies on at least the highest strength	
If the nonlinearity is characterized by less than proportional increases in AUC with increasing dose and results from saturable absorption, conduct the <i>in vivo</i> studies on the lowest strength	
If the nonlinearity is reflected as less than proportional increases in AUC with increasing dose due to limited solubility of the active pharmaceutical ingredient, conduct <i>in vivo</i> studies on two strengths	
Canada requests a fasting study on the lowest strength and a fasting and fed study on the highest strength	
EMA requests a fasting and fed study on one strength and a fasting or fed study (justified based on previous knowledge and PK) on a second strength; the second strength should be the one most sensitive to detect a difference between products	
USA: the strength to be used depends upon the type of nonlinearity	
If the nonlinearity is characterized by greater than proportional increases in AUC with increasing dose, conduct the BE studies on at least the highest therapeutic dose (38)	
If the nonlinearity is characterized by less than proportional increases in AUC with increasing dose and results from saturable absorption, conduct the <i>in vivo</i> studies on the lowest strength (39)	
WHO: Generally the marketed strength with the greatest sensitivity to BE assessment should be administered as a single unit	
Analytes to be measured in biological fluids	
Similarities	All request
Measuring and requiring the parent drug to meet BE limits unless the parent cannot be reliably measured; and	
Measuring and requiring the major metabolite(s) to meet BE limits when the parent cannot be reliably measured	
Differences	Some provide additional reasons for measuring metabolites in biological fluids, and differ in recommending how test and reference metabolite concentrations should be statistically compared, as follows:
Brazil: measure and perform BE testing on metabolites which are	
Formed primarily by presystemic metabolism; and	
Contribute meaningfully to safety and efficacy	
Canada: quantification of metabolite levels may sometimes be helpful; for example, to explain extreme values caused by metabolite changes within a subject	
EMA: using the metabolite as a surrogate for an active parent drug is expected to be accepted only in exceptional cases; the applicant should present any available data supporting the view that	
The metabolite exposure reflects parent drug	
Metabolite formation is not saturated at therapeutic doses	
Japan: Major active metabolites may be measured instead of the unchanged active ingredient, if it is rational	
Singapore/ASEAN: With justification, BE determination can be based on metabolites when	
The metabolite significantly contribute to the net activity; and	
The pharmacokinetic system is non-linear	
South Korea: measure and perform BE testing on active metabolites	
USA: perform summary statistics only and use as supportive data when metabolites are	
Formed primarily by presystemic metabolism; and	
Contribute meaningfully to safety and efficacy.	
WHO: measure and perform BE testing on metabolites when	
The parent is a pro-drug; or	
The metabolites are formed primarily by presystemic metabolism and contribute meaningfully to safety and efficacy	
Add-on, group-sequential, adaptive designs	
Similarities	Very few jurisdictions/organizations recommend these types of designs
Group-sequential and adaptive designs are recommended when the proposed estimate of the within-subject variability has large uncertainty.	
In a group-sequential design	
The overall Type I error and stopping criteria are clearly defined prior to starting the study; and	
The analysis of the first stage is treated as an interim analysis and both analyses are conducted at adjusted significance levels	
In an adaptive design, the second state sample size is based on the estimated within-subject variance from the first stage	
“Add-on” or “additional” studies are recommended when the first (preceding) study fails to meet BE limits	
In an appropriately designed add-on or additional study, data from the preceding BE study and add-on or additional study may be combined for statistical analysis, provided that	
Only one add-on or additional study is conducted;	
The add-on or additional study uses the same protocol as the preceding study;	
There are no fundamental differences between the first (preceding) BE study and add-on study with respect to formulation, design, and subjects; and	
The number of subjects to be included in the add-on or additional study is restricted	
Differences	Australia: the most conservative of the approaches proposed in the literature, the Bonferroni correction, should be applied.
This corresponds to the calculation of 95%, rather than 90%, confidence intervals	
Brazil, China, Chinese Taipei, Mexico, Singapore/ASEAN, WHO: do not mention/specify	
Canada will accept a two-stage group-sequential BE study, provided that the plan to use a two-stage approach and adjusted significance levels is pre-defined in the protocol	
Recommends that the same alpha of 0.0294 be used for both stages (40)	

Table III. (continued)

Canada (41), USA: Will accept a two-stage adaptive design BE study, provided that the intent to use the approach is predefined in the protocol
EMA: Will accept two-stage group-sequential design BE studies, provided that the plan to use a two-stage approach and adjusted significance levels is predefined in the protocol
Japan will accept add-on studies, provided that Not less than half the number of subjects in the initial study can be added-on The “study” is added to the statistical model as a source of variation
South Korea will accept an additional trial; provided that The additional trial uses at least 12 subjects per group The ratio of the mean square error from the ANOVAs of the preceding BE study and the additional trial should be smaller than the top 5% of an <i>F</i> -distribution with a corresponding degree of freedom; and The protocol should clearly state that additional trials were conducted.
USA: will accept two-stage group-sequential design (40–43) BE studies, provided that the plan to use a two-stage approach and adjusted significance levels is predefined in the protocol

parameters in a BE study are the area under the drug concentration versus time profile until the last sampling time (AUC_{0-t}), the area under the drug concentration versus time profile extrapolated to infinity (AUC_{∞}), C_{max} , T_{max} , the drug half-life ($T_{1/2}$) in the biological fluid assayed, and the drug elimination rate constant (k_{el}). All use noncompartmental analysis to calculate the above PK parameters. In addition, all perform $\ln$ transformation on AUC and C_{max} , and use the two one-sided tests procedure (50), performed at the 5% level of significance, to determine if the 90% CI of the test/reference AUC and C_{max} GMRs meet BE limits. All require the 90% CI of the test/reference GMR to meet BE limits of 80–125% for AUC_{0-t} (there are differences in the number of decimal places used for the 90% CI calculations, as will be explained below). Chinese Taipei, Japan, South Korea, and the USA require AUC_{∞} to meet BE limits.

All recommend BE study design modifications for long $T_{1/2}$ drugs. Interestingly, only Brazil formally defines a “long elimination $T_{1/2}$ ” as greater than 24 h. All permit truncation of AUC, although the truncation time varies somewhat from jurisdiction to jurisdiction. In addition, all note that a parallel study design may be considered for long $T_{1/2}$ drugs.

The jurisdictions and organizations vary in methods for statistically comparing test and reference C_{max} . Canada requires the C_{max} GMR (or “point estimate”) to fall within 80–125%. All others impose BE limits on the 90% CI of the test/reference C_{max} GMRs, although they vary in how the C_{max} BE limits are set. Brazil, the EMA, Japan, Mexico, and South Korea require C_{max} to meet BE limits of 80–125%. China uses limits of 70–143%. Chinese Taipei, Singapore/ASEAN, and the WHO specify that ordinarily, C_{max} should meet limits of 80–125%, but when safety and efficacy concerns are justified, 75–133% may be considered with prior approval.

For steady-state BE studies, all require the 90% CIs of the test/reference GMRs to meet BE limits of 80–125% for AUC_{τ} (AUC over the dosing interval). For C_{maxSS} (C_{max} at steady state), all require the 90% CIs of the test/reference GMRs to meet BE limits of 80–125%, with the exception of Canada, which requires that the GMR for C_{maxSS} fall within 80–125% (as is required for C_{max}). In addition, all request noncompartmental calculation of T_{maxSS} (T_{max} at steady state), C_{minSS} (trough drug concentrations at steady state), C_{avgSS} (average steady-state drug concentrations), and percent fluctuation

$\left[\frac{(\text{peak concentration} - \text{trough concentration})}{\text{peak concentration}} \times \text{peak concentration} \right]$. The EMA requires C_{minSS} to meet BE limits of 80–125%; Canada requires that the test/reference ratio for C_{minSS} should not be <80.0% inclusive; and China requests evaluation of fluctuation on a case-by-case basis.

With respect to the number of decimal places considered in the BE statistical calculations, Brazil, China, Chinese Taipei, Japan, Mexico, Singapore/ASEAN, South Korea, and the WHO specify that the limits are 80–125%; Canada specifies 80.0–125.0%; the EMA and USA specify 80.00–125.00%.

Most jurisdictions and organizations evaluate T_{max} if it is determined that this parameter is clinically relevant. They differ in how T_{max} is evaluated in such circumstances. Brazil, China, Japan, Singapore/ASEAN, South Korea, and the WHO apply nonparametric analysis to statistically compare test and reference T_{max} . The EMA and USA (51) state that the regulators will evaluate whether differences between test and reference T_{max} values are clinically significant.

Highly Variable Drugs

HV drugs are defined as drugs in which the within-subject variability (% CV) in one or more of the BE measures (AUC, C_{max}) is 30% or greater (52,53). Determining BE of HV drugs is challenging because, due to the high variability, it may be necessary to enroll large numbers of subjects to provide adequate power in order that a two-way study of two BE products will be acceptable (54).

As shown in Table VI, jurisdictions/organizations use a variety of approaches to reduce the number of subjects needed for an acceptable study of two bioequivalent HV drugs. Several permit widening BE limits for C_{max} if previously established in the study protocol and if scientifically justified. As previously mentioned, Japan, Singapore/ASEAN, and the WHO suggest using a steady-state BE study design to reduce variability. Japan also recommends using studies with stable isotopes for HV drugs that may require large sample sizes in the BE studies. The EMA and USA recommend a reference-scaled average BE (RSABE) approach. In the RSABE approach, the reference product is administered twice in the study (either a three- or four-way design is acceptable), and the acceptance limits scale based on

Table IV. Similarities and Differences in BE Study Type for Various Dosage Forms

Immediate-release (IR) solid oral dosage forms	
Similarities	All request a single-dose bioequivalence study under <i>fasting</i> conditions; and Most do not request a <i>fed</i> bioequivalence study for IR dosage forms, with exceptions listed below
Differences	Some request a fed study for IR products, as follows: Brazil: when there is a known food interaction Canada: when there is a serious safety risk to subjects in the presence of food EMA: where the Summary of Product Characteristics (SPC) states it should only be taken with food then study under <i>fed</i> conditions Singapore/ASEAN: Where SPC contains specific recommendations in relation to food intake the study should be designed accordingly USA: a fed bioequivalence study should always be conducted for IR formulations, with the following exceptions When reference product labeling recommends taking on an empty stomach When test and RLD product are rapidly dissolving, have similar dissolution profiles and contain a drug substance with high solubility and high permeability
Fed BE study for modified-release (MR) solid oral dosage forms	
Similarities	All request single-dose BE studies under <i>fasting</i> and <i>fed</i> conditions, with exceptions listed below
Differences	Singapore/ASEAN: In accordance with the SPC and/or specific guidelines
Composition of meal used in fed BE studies	
Similarities	Jurisdictions either (1) recommend a particular meal composition; or (2) do not specify
Differences	Brazil, China, Mexico, Singapore/ASEAN: no recommendations about meal composition Canada, EMA, USA: 800–1,000 kcal of which 50% is fat, administered 30 min prior to dosing Chinese Taipei: high fat, high Kcal meals Japan: 700 kcal of which no more than 20% by energy is lipid, administered 30 min prior to dosing South Korea: high-fat meal, administered 30 min prior to dosing WHO: meal should be based on local custom and diet, administered 30 min prior to dosing
Multiple-dose studies	
Similarities	In general, all request multiple-dose BE studies in certain situations, especially for BE studies using patients; other reasons for requesting multiple-dose BE studies differ
Differences	Brazil: can be used in cases in which they recognizably reduce inter-individual variability in the absorption of the active ingredients Canada: may be considered for MR formulations China, EMA, South Korea: for MR dosage forms Chinese Taipei lists the following situations: MR dosage forms Drugs that exhibit nonlinear kinetics at steady-state Japan: multiple-dose studies or studies with stable isotopes may be useful for highly variable drugs that require large sample sizes Singapore/ASEAN lists the following situations In accordance with specific guidance Drugs that exhibit non-linear kinetics at steady-state WHO lists the following situations: Drugs that exhibit non-linear kinetics at steady-state Cases where assay sensitivity is too low to adequately characterize PK profile after a single dose Extended-release (ER) dosage forms with a tendency to accumulate
Suspensions	
Similarities	All recommend that <i>in vivo</i> BE studies should always be conducted for systemically active formulations; several jurisdictions highlight oral suspension products
Differences	Singapore/ASEAN, USA: same types of <i>in vivo</i> studies are required as for tablets and capsules
Non-oral formulations	
Similarities	All recommend that <i>in vivo</i> studies should always be performed for systemically active formulations; several jurisdictions provide specific recommendations for transdermal products as shown below
Differences	EMA, for transdermal products: Single- and multiple-dose BE studies The site of application should be in the same body area for the test and reference product Use a replicate study design if the test and reference use different release mechanisms (for example, a reservoir versus a matrix) Compare test and reference adhesion, local irritation, sensitization, and photo-toxicity (44) USA, for transdermal products: Single-dose BE studies Compare test and reference adhesion, local irritation, sensitization

the within-subject variability of the reference product. Both the EMA and USA impose a GMR constraint when using RSABE for HV drugs. As shown in Table VI, aside from the above similarities, the EMA and USA implement RSABE in different ways. In addition, the EMA only permits RSABE to

be used for $C_{\max}$, whereas the USA will accept RSABE for both AUC and $C_{\max}$. Australia will consider using the EMA RSABE approach for BE studies of HV drugs provided that (1) the drug has highly variable PK due to incomplete or variable absorption or substantial (>40%)

Table V. Similarities and Differences in PK Parameter Determination and BE Statistics

Single-dose fasting and fed BE studies	
Similarities	All
	Use noncompartmental analysis to determine AUC_{0-t} , AUC_{∞} , C_{max} , and T_{max} , $T_{1/2}$, and k_{el} for single-dose studies
	Perform log-transformation on AUC and C_{max}
	Calculate test/reference GMRs for AUC and C_{max}
	Use analysis of variance (ANOVA) and the two one-sided tests procedure, performed at the 5% level of significance, to determine if the 90% CIs of the test/reference GMRs meet BE limits
	Require AUC_{0-t} to meet 80–125% limits
Differences	Chinese Taipei, Japan, Singapore/ASEAN, South Korea, USA: 80–125% limits for AUC_{∞}
	Brazil, EMA, Japan, Mexico, South Korea, USA: 80–125% limits for C_{max}
	Canada: the test/reference GMR for C_{max} should fall within 80–125%
	China: 70–143% limits for C_{max}
	Chinese Taipei, Singapore/ASEAN, WHO: for C_{max} , ordinarily, 80–125% limits should be applied, but 75–133% limits may be considered with prior approval when safety and efficacy concerns are justified
	Japan, South Korea: products that do not meet BE acceptance limits may still be deemed bioequivalent provided that <i>all</i> of the following three criteria are met
	1. The total sample size of the initial study is not <20
	2. The GMRs for AUC and C_{max} are within 0.9 to 1.11
	3. <i>In vitro</i> dissolution behavior of the test and reference products is deemed to be the same under all conditions tested
Long half-life drugs	
Similarities	All permit truncation of AUC, to replace AUC_{0-t}
Differences	Brazil, Canada, EMA, Japan, USA, WHO: truncation to 72 h
	China, Singapore/ASEAN: for long half-life drugs, can truncate AUC to adequately ensure comparison of absorption process
	Chinese Taipei: for long half-life drugs, can truncate AUC if necessary, with prior approval
Steady-state BE studies	
Similarities	All
	Determine AUC_{τ} , C_{maxSS} , T_{maxSS} , C_{minSS} , C_{avgSS} , % fluctuation via noncompartmental methods
	Perform log-transformation on AUC_{τ} and C_{maxSS}
	Calculate test/reference GMRs
	Use analysis of variance (ANOVA) to determine if the 90% CIs of the test/reference GMRs meet BE limits; and
	Require AUC_{τ} , C_{maxSS} to meet 80–125% BE limits
Differences	EMA: in addition, C_{minSS} should meet bioequivalence limits of 80–125%
	Canada: the test/reference ratio for C_{min} should not be <80% inclusive
	China: include evaluation of fluctuation is a case-by-case determination
Evaluation of T_{max}	
Similarities	Most jurisdictions compare test and reference T_{max} values, with exceptions listed below
Differences	Brazil, China, Japan, Singapore/ASEAN, South Korea, WHO: nonparametric analysis applied to non-transformed data, only if T_{max} is judged to be clinically relevant
	South Korea: limits should be 80–125%
	Brazil, Japan, China, Singapore/ASEAN, WHO: limits should be a clinically determined range
	Canada: for drugs for which an early time of onset of action is important for therapeutic effects, the relative mean area under the curve to reference product T_{max} ($AUC_{TmaxRef}$) should meet limits of 80–125% inclusive
	Chinese Taipei: not mentioned/specified
	EMA: if rapid release is claimed to be clinically relevant and of importance for onset of action or related to adverse events, there should be no apparent difference in T_{max} and its variability between test and reference products
	USA: if differences in T_{max} are judged to be clinically relevant, this may provide evidence that the test and reference products are not therapeutically equivalent (49)

first-pass metabolism and (2) the reference product is one marketed in Australia. Finally, Canada states that there is no compelling need for a distinct category of HV drugs.

Narrow Therapeutic Index Drugs

NTI drug products are generally defined as those products containing certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring and/or where product labeling indicates a narrow therapeutic range designation (56). Other terminologies commonly used to refer to drugs with a narrow therapeutic index are “critical dose drugs” (57) and “narrow therapeutic range (NTR) drugs” (11,58). Different regulatory agencies

use the terms “narrow therapeutic index,” “narrow therapeutic range,” and “critical dose” to designate drugs for which there is a narrowly defined plasma concentration range between risk and benefit. At present, the definitions of these three terms are basically the same across various regulatory agencies. The term “narrow therapeutic index” drugs or “NTI” drugs will be used throughout the remainder of this article; however, it is interchangeable with the terms “narrow therapeutic range” drugs and “critical dose” drugs.

The jurisdictions and organizations differ in recommendations of how to design and evaluate BE studies of generic NTI drugs. As shown in Table VII, Australia, Canada, China, Singapore/ASEAN, EMA, Japan, South Korea, Switzerland, and the WHO use more stringent acceptance limits for NTI

Table VI. Similarities and Differences in Approaches for BE Studies of HV Drugs

Highly-variable drugs	
Similarities	All recommend Crossover or parallel study designs Noncompartmental analysis to determine PK parameters ANOVA, performed at the 5% level of significance, on the GMRs
Differences	Australia: as follows: If the generic drug has highly variable PK due to incomplete or variable absorption or substantial (>40%) first-pass metabolism, then the reference product must be one marketed in Australia If this criterion is met then follow the EMA recommendations for HVD BE studies Brazil: a wider BE acceptance limit may be applied to $C_{\max}$ if previously established in the study protocol and if scientifically justified Chinese Taipei, South Korea: do not specify/mention Canada: no compelling need for a distinct category of HV drugs Singapore/ASEAN, WHO: one of the following approaches can be used: In rare cases, a wider BE limit acceptance range may be applied to AUC and $C_{\max}$, if based on sound clinical justification A steady-state BE study can be conducted to reduce variability EMA: a RSABE approach may be applied to $C_{\max}$ only. A brief summary of study design and acceptance criteria is as follows: The reference product should be administered at least twice to determine within-subject variability Either a 3- or 4-period replicate design study is acceptable BE limits are scaled to the within subject variability of the reference product The $C_{\max}$ GMR in the study should fall within 0.80–1.25 The within-subject %CV and corresponding BE limits are shown below

Within-subject CV (%)	BE limits
30	80.00 125.00
35	77.23 129.48
40	74.62 134.02
45	72.15 138.59
≥50	69.84 143.19

Japan: one of the following approaches may be used to reduce variability:

For drugs with a wide therapeutic index, it may be appropriate to set BE limits wider than 80–125% for $C_{\max}$

A steady-state BE study

A study with stable isotope

USA: a RSABE approach may be applied to AUC and $C_{\max}$ (55). A brief summary of study design and acceptance criteria is as follows:

The reference product should be administered at least twice to determine within-subject variability

Either a 3- or 4-period replicate design study is acceptable; The AUC and $C_{\max}$ GMRs in the study should fall within 0.80 to 1.25

BE limits are scaled to the within subject variability of the reference product, but not until the within-subject standard deviation of the reference product (s_{WR}) is ≥ 0.294 ; and

A 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta s_{WR}^2$ must be ≤ 0 , where

μ_T =test product mean

μ_R =reference product mean

$\theta = \frac{(\ln \Delta)^2}{\sigma_{w0}^2}$

$\Delta=1.25$

$\sigma_{w0}=0.25$

drugs. In Brazil, Chinese Taipei, and Mexico, BE limits for NTI drugs are not different from those for other drugs. The USA recently began to recommend a more stringent acceptance limit for some NTI drugs.

Canada and Japan refer to NTI drugs as critical dose drugs and NTR drugs, respectively; both provide definitions in their respective guidelines (see Table VII). The EMA concludes that it is not possible to define a set of criteria to categorize drugs as NTI and recommends deciding on a case-by-case basis. The USA recently proposed a RSABE approach for these products (60–62). A RSABE approach should have the effect of narrowing the BE limits for NTI drugs. As BE acceptance limits scale based on the variability of the reference drug, and most NTI drugs have low within-

subject variability, use of reference scaling will in effect narrow the BE limit acceptance range. As NTI drugs generally have low within-subject variability, such an approach will effectively narrow the BE limits. The USA also proposed narrowing the assayed potency specifications for the finished products; this latter approach is already in effect for levothyroxine tablets (63).

Conditions Under Which Biowaivers may be Granted

Table VIII shows similarities and differences in the biowaiver process. All permit the waiving of BE study requirements for products for which BE is self-evident. This includes solutions for parenteral, oral, or local use. There are

Table VII. Similarities and Differences in BE Study Designs and Acceptance Limits for NTI Drugs

Critical dose drugs/Narrow therapeutic index drugs	
Similarities	Most jurisdictions/organizations that use more stringent BE acceptance limits for NTI or “critical dose” drugs, some provide lists of drugs to which the more stringent BE limits should apply
Differences	<p>Australia: imposed the following restrictions: Generic NTI drugs must be compared to a reference drug product marketed in Australia If this criterion is met, then follow the EMA Guidelines with respect to other restrictions on BE studies of generic NTI drugs</p> <p>Brazil, Chinese Taipei, Mexico: do not specify/mention</p> <p>Canada: recommends the following for critical-dose drugs: Provides a list Defines critical dose drugs as 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 For critical-dose drugs, the 90% CI for AUC should be within 90.0–112.0 inclusive For critical-dose drugs, 90% CI for C_{max} should be within 80.0–125.0 inclusive</p> <p>China, Singapore/ASEAN, WHO: in the case of an especially narrow therapeutic range, the BE limits may need to be tightened based on clinical justification</p> <p>EMA: recommends the following for NTI drugs: In specific cases of NTI drugs, the acceptance interval for AUC should be tightened to 90.00–111.11%. Where C_{max} is of particular importance for safety, efficacy, or drug level for monitoring the 90.00–111.11% acceptance interval should also be applied for this parameter It is not possible to define a set of criteria to categorize drugs as NTI Therefore, it must be decided on a case-by-case basis if an active substance is NTI based on clinical considerations</p> <p>Japan: recommends the following for NTR drugs: Provides a list Defines NTR drugs as those having a less than twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood For NTI drugs, the acceptance interval for AUC and C_{max} should be tightened to 90.00–111.11% (59) Imposes more stringent BE requirements for certain types of postapproval manufacturing process/site, or formulation changes</p> <p>South Korea: Recommends the following for NTI drugs Provides a list BCS biowaivers cannot be applied to NTI drugs Imposes more stringent types of BE requirements for certain types of postapproval manufacturing process/site, or formulation changes</p> <p>USA: current Guidance for Industry recommends that BE limits of 80–125% be applied to AUC and C_{max} for NTI drugs BCS biowaivers cannot be applied to NTI drugs; and More stringent types of BE requirements are imposed on certain types of postapproval manufacturing process/site, or formulation changes</p> <p>In 2011, FDA presented a proposal on BE requirements for generic NTI drugs before its Advisory Committee; the Committee agreed with the proposal summarized below, which is still under development Develop a regulatory definition of NTI and post for notice and comment Require assayed potency specifications of 95–105% Use RSABE to scale the BE limits to the within-subject variability of the reference product, in cases where within-subject variability <20% If within-subject variability $\geq 20\%$, then use BE limits of 80–125% Develop statistical methods to assure that within-subject variability of generic product does not exceed that of reference product Post these recommendations for NTI drugs as Specific Products Bioequivalence Guidance for Industry on a case-by-case basis</p>

generally additional criteria to be met before a biowaiver can be granted. Test and reference solutions intended for parenteral use should have the same active and inactive ingredients in the same amounts; generic solutions intended for oral or topical use should not contain excipients that could potentially cause differences in drug substance absorption. All will consider granting biowaivers for non-biostudy strengths of solid dosage forms, provided that certain requirements are met [proportional similarity across strengths; acceptable *in vitro* dissolution or *in vitro* drug release from the formulation; acceptable BE study on the bio-study strength(s)]. The USA does not grant biowaivers for MR

products, but may deem non-biostudy strengths BE to corresponding strengths subject to certain criteria (64). This policy applies to all MR dosage forms, including but not limited to delayed-release tablets and capsules, extended-release tablets, transdermal products, injectable suspensions, and injectable implants.

Use of the Biopharmaceutics Classification System to Grant Biowaivers

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal

Table VIII. Similarities and Differences for Granting Biowaivers

Solutions	
Similarities	All permit biowaivers for solutions intended for parenteral, oral, or local use Solution formulations intended for parenteral use should have the same active and inactive ingredients in the same amounts (i.e., be qualitatively and quantitatively, Q1/Q2, the same) If the solution is to be administered orally or topically, the test product should not be formulated in such a manner that would cause drug absorption to differ between the test and reference products
Differences	None in this regard
Non-biostudy strengths of a solid dosage form product line	
Similarities	All permit biowaivers for non-biostudy strengths of a solid dosage form, provided that three conditions are met BE is demonstrated <i>in vivo</i> for at least one strength <i>In vitro</i> dissolution testing is acceptable; and Strengths considered for the biowaiver are proportionally similar to the strength that underwent acceptable <i>in vitro</i> testing
Differences	All use the f_2 (similarity factor) metric to compare dissolution profiles USA: published a document describing acceptability of evidence of <i>in vivo</i> proportionality if various strengths of a product line are not compositionally proportional (64) South Korea: linear elimination kinetics should be established over those approved therapeutic dose ranges
BCS-based biowaivers	
Similarities	Those jurisdictions/organizations that consider granting BCS-based biowaivers will not consider granting these for Buccal, orally disintegrating, or MR solid oral dosage forms NTI drugs Generic drug IR formulations under consideration for BCS-based class I biowaivers should not contain any excipients that can impact drug absorption
Differences	Brazil, Chinese Taipei, Mexico, Japan: do not grant BCS-based biowaivers at present China, Singapore/ASEAN, South Korea, USA: will consider granting biowaivers for BCS class I drugs EMA, WHO: will consider granting biowaivers for BCS Class I and BCS class III drugs Canada: a draft guidance available for public comment proposes that biowaivers can be granted for BCS class I and III drugs

permeability (65). When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms; these factors are dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

- Class 1: high solubility–high permeability
- Class 2: low solubility–high permeability
- Class 3: high solubility–low permeability
- Class 4: low solubility–low permeability.

Within the BCS framework, when certain criteria are met, the BCS can be used as a drug development tool to justify the granting of biowaivers.

Currently, Australia, the EMA, Switzerland, and the WHO (66) will consider granting biowaivers for class I and III drugs. Canada recently issued a draft guidance for industry proposing criteria to be met for the granting of class I and III biowaivers (67). South Korea and the USA will consider granting biowaivers for class I drugs. Regarding Singapore and China, the ASEAN Consultative Committee for Standards and Quality primarily considers the BCS criteria when evaluating applications for IR solid oral dosage forms, whereas China will consider granting BCS biowaivers for class I drugs undergoing postapproval changes (68). All jurisdictions and organizations that consider granting BCS biowaivers stipulate that such biowaivers are not applicable to NTI drugs.

The WHO, under the PQP, which provides a stringent regulatory function for medicines, posted a supplementary guidance document on BCS biowaivers; this is the document currently used to evaluate drug products (66). The WHO also posts a general guidance on the topic of BCS-based

biowaivers (35). The general guidance provides information on the WHO position on BCS biowaivers and may be used as a guide for national regulatory authorities developing positions on this subject.

Japan maintains that formulation and manufacturing, rather than solubility and permeability, are indicative of bioequivalence (68). In addition, Japan notes that dissolution testing is already extensively applied in drug regulatory submissions, and that since permeability is not known for many drugs, it is difficult to use BCS to establish regulatory bioequivalence.

For the jurisdictions and organizations that formally implement the BCS, Table IX shows what types of data should be submitted to support class I and III biowaivers.

CONCLUSION

BE studies are an important part of the generic drug approval process throughout the world. This review focused on the BE study requirements and regulatory specifications among a number of worldwide jurisdictions and organizations. Although there are important differences in BE approaches throughout the various regulatory agencies investigated in this article, we observed that, in general, there are many more similarities. This is particularly the case with respect to general BE study design, methods of calculating key PK parameters, statistical analysis methods used to verify BE, and criteria necessary for the granting of biowaivers. Identifying the existence of commonalities underlying regulatory evaluation of BE throughout the world is an important first step in working toward global harmonization and convergence of generic drug development.

Table IX. Similarities and Differences in BCS Biowaiver Criteria

Basic criteria for establishing that drug substance is highly soluble				Basic criteria for establishing that drug substance shows high intestinal permeability			
Jurisdiction or organization	Establish high solubility of	pH range	Number of pH values to test	Are <i>in vivo</i> permeability studies acceptable	Are <i>in vitro</i> permeability studies acceptable	Are <i>in vivo</i> or <i>in vitro</i> intestinal permeation studies acceptable	Are literature data acceptable
Canada (draft guidance)	Highest dose	1.2–6.8	At least 3, to encompass pKa region	Yes	No, perhaps as supportive	No	Yes, if acceptable design
EMA	Highest dose	1.2–6.8	At least 3, to encompass pKa region	Yes	No; perhaps as supportive	No	Yes, if acceptable design
South Korea	Highest strength	1–7.5	Depends on ionization profile; should encompass pKa region	Yes	Yes	Yes	Not discussed
USA	Highest strength	1–7.5	Depends on ionization profile; should encompass pKa region	Yes	Yes	Yes	No; perhaps as supportive
WHO	Highest dose	1.2–6.8	At least 3	Yes	Yes	Yes	Not discussed
All follow these criteria	Volume = 250 mL Temperature = 37 ± 1°C Use shake flask or similar method			<i>In vivo</i> intestinal permeation studies can use humans or animals <i>In vitro</i> intestinal permeation studies can use human or animal tissue <i>In vitro</i> permeability studies use epithelial cell monolayers If <i>in vitro</i> systems are used Should provide evidence that drug substance is stable in the gastrointestinal tract If the drug is a prodrug which is converted to an active metabolite before intestinal absorption, should conduct <i>in vitro</i> permeability studies on metabolite			

Basic criteria for establishing that product is rapidly dissolving or very rapidly dissolving				Restrictions on how excipients can vary from test to reference product			
Jurisdiction or organization	Optimal paddle speed	Optimal basket speed	Criteria for rapid dissolution	Criteria for very rapid dissolution	Class I	Class III	
Canada (draft guidance)	Should be 50	Should be 100	>85% in 30 min	>85% in 15 min	Recommend Q1 same, Q2 very similar, but test and reference excipients may differ	Should be Q1 same, Q2 very similar	
EMA	Usually 50	Usually 100	>85% in 30 min	>85% in 15 min	Recommend Q1 same, Q2 very similar, but test and reference excipients may differ	Should be Q1 same, Q2 very similar	
South Korea	Should be 50	Should be 100	>85% in 30 min	>85% in 15 min	Use well-established excipients in usual amounts	Does not grant biowaivers for class III	
USA	Should be 50	Should be 50	>85% in 30 min	Not defined	Use well-established excipients in usual amounts	Does not grant biowaivers for class III	
WHO	Should be 75	Should be 100	>85% in 30 min	>85% in 15 min	Use well-established excipients in usual amounts	Should be Q1 same, Q2 very similar	
All follow these criteria	Volume = at least 900 mL Temperature 37 ± 1°C (Canada, EMA, USA) 37 ± 0.5°C (South Korea, WHO) At least 3 pH values, pH 1.2, 4.5, 6.8 (South Korea recommends pH 4.0 rather than pH 4.5) Surfactants are not permissible At least 12 units each of test and reference product Should use <i>f</i> ₂ metric for profile comparison, unless dissolution is very rapid				Differences between test and reference excipients are only acceptable for class I		

ACKNOWLEDGMENTS

The authors wish to thank the following for valuable contributions to this manuscript: Gary Condran, Craig Simon, Bindu Islam, and Mike Ward of Health Canada; Silvia Arteaga Hernandez of the Federal Commission for the Protection Against Sanitary Risk, Mexico; Jun Kitahara and Nobumasa Nakashima of the Japanese Pharmaceuticals and Medical Devices Agency; Cordula Landgraf and Gabriela Zenhausern of SwissMedic; and Matthias Mario Stahl of the World Health Organization; and Xiaofei (Sophie) Wang of FDA's Office of Generic Drugs.

REFERENCES

1. Understanding generic drugs. US Food and Drug Administration, Silver Spring, 2012. <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm>. Accessed 5 Apr 2013.
2. Mastan S, Latha TB, Ajay S. The basic regulatory considerations and prospects for conducting bioavailability/bioequivalence studies—an overview. *Comp Eff Res*. 2011;1:1–25. doi:10.2147/CER.S15861.
3. Kanfer I. Introduction. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 1–16.
4. Electronic orange book. US Food and Drug Administration, Silver Spring, 2012. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>. Accessed 5 Apr 2013.
5. Guideline, the investigation of bioequivalence. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA) 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 5 Apr 2013.
6. US Government Printing Office. *Federal Food Drugs and Cosmetic Act. Drugs and devices. Chapter 9, Section 355(j)(8)(B)(i). Title 21 United States Code*. 2011.
7. Chen ML, Shah V, Patnaik R, Adams W, Hussain A, Conner D, *et al.* Bioavailability and bioequivalence: an FDA regulatory overview. *Pharm Res*. 2001;18:1645–50.
8. US Food and Drug Administration Response to Dockets No. FDA-2010-P-0111 and FDA-2008-P-9-057, establishing bioequivalence to mesalamine delayed-release tablets and mesalamine extended-release capsules. <http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0111-0011>. Accessed 5 Apr 2013.
9. US Food and Drug Administration Response to Docket No. FDA-2012-P-0779, 2012, concerning the bioequivalence requirements applicable to abbreviated new drug applications (ANDAs) referencing acyclovir ointment. <http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0779-005>. Accessed 5 Apr 2013.
10. Section 320.22. Criteria for waiver of evidence of in vivo bioavailability or bioequivalence. In: Title 21 of the Code of Federal Regulations. 57 FR; 1992. p. 17998, as amended at 67 FR; 2002. P. 77673.
11. Guidance for Industry, bioavailability and bioequivalence studies for orally-administered drug products—general considerations. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2003. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf>. Accessed 5 Apr 2013.
12. Mansour G. Experience of regulatory harmonization in Canada: participation in international regulatory cooperation. In: *Proceedings of the African Medicines Regulatory Harmonization (AMRH) Stakeholders Consultation*, 29 March 2012, Arusha, Tanzania. <http://www.amrh.org>. Accessed 5 Apr 2013.
13. Pharmaceutical and Medical Devices Agency, Japan. The meeting of IGDRP held December 3 to 4. PMDA Updates, January 2013. http://www.pmda.go.jp/english/international/pdf/update/updates_201301_e.pdf. Accessed 5 Apr 2013.
14. Australian Regulatory Guideline on Over-the-Counter Medicines (ARGOM) Appendix I, Section 6, generic products. Australian Government Department of Health and Ageing Therapeutic Goods Administration 2012. <http://www.tga.gov.au/industry/otc-argom-app1-06-generic.htm>. Accessed 5 Apr 2013.
15. Annex, guide for relative bioavailability/bioequivalence tests of medicines, Brazilian National Agency for Sanitary Surveillance (ANVISA) 2003. http://www.anvisa.gov.br/eng/legis/resol/896_29_05_03_re_e.htm. Accessed 5 Apr 2013.
16. Guideline, for bioavailability/bioequivalence studies, Taiwan Department of Health (DOH) Food and Drug Administration 2009. <http://www.cde.org.tw/English/Regulations/SubLink/Document%2004.pdf>. Accessed 5 Apr 2013.
17. Guidelines for submission of research protocols to demonstrate the drug interchangeability. The Mexican Federal Commission for the Protection Against Sanitary Risk (COFEPRIS) 2012. <http://www.cofepris.gob.mx/Paginas/Inicio.aspx>. Accessed 5 Apr 2013.
18. Guidelines for the implementation of the standard NOM-177-SSA1-1998 establishing tests and procedures for demonstrating that a product is interchangeable. The Mexican Federal Commission for the Protection Against Sanitary Risk (COFEPRIS) 2012. <http://www.cofepris.gob.mx/Paginas/Inicio.aspx>. Accessed 5 Apr 2013.
19. BABEC Ing. Helmut Schütz, Guidelines and guidance documents, Vienna. <http://bebac.at/Guidelines.htm>. Accessed 5 Apr 2013.
20. Administrative Ordinance: Application and Authorization for Generics. Swiss Agency for Therapeutic Products (Swissmedic), Geneva, Switzerland 2012. <http://www.swissmedic.ch/suchen/index.html>. Accessed 5 Apr 2013.
21. Regulatory guidelines on prescription medicines, Appendix 15, Biopharmaceutics studies. Australian Government Department of Health and Ageing, Therapeutic Goods Administration 2012. <http://www.tga.gov.au/pdf/pm-argpm-ap15.pdf>. Accessed 5 Apr 2013.
22. Hung CT, Ren D, Folland LA, Lam FC, Hung NA, Smart R. Australasia. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 17–45.
23. Marques MRC, Storpitis S, Bueno MM. Brazil. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 48–66.
24. McGilveray IJ. Canada. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 67–94.
25. Guidance Document, conduct and analysis of comparative bioavailability studies. Health Canada Therapeutic Products Directorate Bureau of Policy, Science, and International Programs 2012. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.pdf. Accessed 5 Apr 2013.
26. Guidance: bioavailability and bioequivalence studies for chemical drug products. People's Republic of China State Food and Drug Administration 2005. <http://eng.sfda.gov.cn/WS03/CL0755>. Accessed 5 Apr 2013.
27. Pao LH, Chi JF, Hu OYP. Taiwan. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 232–53.
28. Riku J. Japan. In: Kanfer I, Shargel L, editors. *Generic drug product development, international regulatory requirements for bioequivalence*. New York: Informa Healthcare; 2010. p. 164–82.
29. National Institute of Health Sciences Guideline, bioequivalence studies of generic products. Japanese Pharmaceutical and Food Safety Bureau, Minister of Health, Labor and Welfare, 2012 [http://www.nihs.go.jp/drug/be-guide\(e\)/Generic/GL-E_120229_BE.pdf](http://www.nihs.go.jp/drug/be-guide(e)/Generic/GL-E_120229_BE.pdf). Accessed 5 Apr 2013.
30. Fandaño AL. New Mexican marketing authorization and data exclusivity regulations. IP in the Life Sciences Industries 2008.

- <http://www.iam-magazine.com/issues/article.aspx?g=49b1bfeb-ca52-4235-a390-8947ceb3287e>. Accessed 24 Nov 2012.
31. Mexico's health law regulations for health consumables, Article 2. XIV, as amended 2 January 2008.
 32. Guidelines, for the conduct and bioavailability and bioequivalence studies. Association of Southeast Asian Nations (ASEAN) Consultative Committee for Standards and Quality (ACCSQ) Pharmaceutical Product Working Group 2004. http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/western_medicines/files_guidelines.Par.59188.File.dat/ACTR_GuidelinesforConductofBioavailabilityandBioequivalenceStudies_Nov05.pdf. Accessed 5 Apr 2013.
 33. Guidance document, Bioequivalence study. Korea Food and Drug Administration 2008. <http://www.kfda.go.kr/eng/index.do?nMenuCode=5>. Accessed 31 Aug 2012.
 34. Modifications to the administrative ordinance, instructions: application and authorisation for generics. Swiss Agency for Therapeutic Products (Swissmedic), Geneva, Switzerland. 2012. <http://www.swissmedic.ch/zulassungen/00173/01407/index.html?lang=en>. Accessed 5 Apr 2013.
 35. Multisource (generic) pharmaceutical products; guidelines on registration requirements to establish interchangeability. Annex 7, WHO Technical Report Series, 937, World Health Organization, 2006. http://www.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937_eng.pdf#page=359. Accessed 5 Apr 2013.
 36. Mexico Embassy Update on Pharmaceutical IPR Issues in Mexico. August 30 2011. <http://dazzlepod.com/cable/07MEXICO3724>. Accessed 5 Apr 2013.
 37. Interview with Socorro España Lomeli, Executive Director of ANAFAM. Pharmaceutical Industries Focus Reports. <http://www.pharma.focusreports.net/index.php#state=InterviewDetail&id=1954>. Accessed 5 Apr 2013.
 38. Guidance for industry, phenytoin extended capsule. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2008. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089476.pdf>. Accessed 5 Apr 2013.
 39. Draft guidance for industry, rifaximin tablet. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2011. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281455.pdf>. Accessed 5 Apr 2013.
 40. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64:191–9.
 41. Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuurmann DJ, *et al*. Sequential design approaches for bioequivalence studies with crossover designs. *Pharm Stat*. 2008;7:245–62.
 42. Clinical pharmacology review of NDA 21154. Drugs@FDA. US Food and Drug Administration Center for Drug Evaluation and Research, Silver Spring, 2001. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21154_Nexium.cfm. Accessed 5 Apr 2013.
 43. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549–56.
 44. Concept paper on the revision of the note for guidance on quality of modified-release oral dosage forms and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation), European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/06/WC500091662.pdf. Accessed 5 Apr 2013.
 45. Guidance for Industry, bioequivalence recommendations for specific products. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2010. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. Accessed 5 Apr 2013.
 46. Guidance for industry, food-effect bioavailability and fed bioequivalence studies. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2002. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>. Accessed 5 Apr 2013.
 47. Guidance for industry, size of beads in drug products labeled for sprinkle. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2012. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240243.pdf>. Accessed 5 Apr 2013.
 48. Note for Guidance, modified-release oral and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation). The European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Unit Committee for Proprietary Medicinal Products (CPMP) 1999. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003126.pdf. Accessed 5 Apr 2013.
 49. Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, *et al*. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Ann Pharmacother*. 2009;43:1583–97.
 50. Schuurmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm*. 1987;15:657–80.
 51. US Food and Drug Administration Response to Docket No. FDA-2001-P-0120-1, establishing bioequivalence to the verapamil hydrochloride extended-release tablet 2003. <http://www.regulations.gov#!documentDetail;D=FDA-2001-P-0120-0001>. Accessed 5 Apr 2013.
 52. Blume HH, Midha KK. Bio-International 92, conference on bioavailability, bioequivalence, and pharmacokinetic studies. *J Pharm Sci*. 1993;82:1186–9.
 53. Shah VP, Yacobi A, Barr WH, Benet LZ, Breimer D, *et al*. Evaluation of highly variable drugs and drug formulations. *Pharm Res*. 1996;13:1590–4.
 54. Patterson SD, Zariffa NMD, Montague TH, Howland K. Non-traditional study designs to demonstrate average bioequivalence for highly variable drug products. *Eur J Clin Pharmacol*. 2001;57:663–70.
 55. Draft guidance for industry, progesterone capsule. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2011. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>. Accessed 5 Apr 2013.
 56. Pope ND. Generic substitution of narrow therapeutic index drugs. *US Pharm*. 2009;34(Generic Drug Review Suppl):12–9.
 57. Guidance document, Comparative bioavailability standards: formulations used for systemic effect. Health Canada Therapeutic Products Directorate Bureau of Policy, Science, and International Programs 2012. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/gd_standards_ld_normes-eng.pdf. Accessed 5 Apr 2013.
 58. Attachment 2 of Division-Notification 0229 of the Pharmaceutical and Food Safety Bureau, Guideline for bioequivalence studies for different strengths of solid oral dosage forms. Japanese Ministry of Health, Labour, and Welfare 2012. [http://www.nihs.go.jp/drug/be-guide\(e\)/strength/GL-E_120229_ganryo.pdf](http://www.nihs.go.jp/drug/be-guide(e)/strength/GL-E_120229_ganryo.pdf). Accessed 5 Apr 2013.
 59. Tamboli AM, Todkar P, Zope P, Sayyad FJ. An overview of bioequivalence: regulatory considerations for generic drug products. *J Bioequiv Bioavail*. 2010;2:86–92.
 60. Summary minutes of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, July 26 2011. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm>. Accessed 5 Apr 2013.
 61. Draft Guidance for Industry, warfarin sodium tablets, US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2012. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf>. Accessed 5 Apr 2013.
 62. Draft guidance for industry, tacrolimus capsules. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2012. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM181006.pdf>. Accessed 5 Apr 2013.

63. Levothyroxine sodium tablets. In: The United States Pharmacopeia (USP 35) The National Formulary (NF 30). Rockville: The US Pharmacopeial Convention; 2012, p. 3679–3681.
64. US Food and Drug Administration Response to Docket No. FDA-2008-P-0185, establishing bioequivalence to the minocycline hydrochloride extended-release tablet 2009. <http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0185-0006>. Accessed 24 Nov 2012.
65. Guidance for Industry, waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2000. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>. Accessed 24 Nov 2012.
66. Guidance document, General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications. World Health Organization Prequalifications of Medicines Programme 2011. http://apps.who.int/prequal/info_applicants/BE/BW_general_2011November.pdf. Accessed 24 Nov 2012.
67. Draft guidance document, Biopharmaceutics classification system based biowaiver. Health Canada Therapeutic Products Directorate Bureau of Policy, Science, and International Programs 2012. http://www.hc-sc.gc.ca/dhp-mpps/alt_formats/pdf/consultation/drug-medic/bcs_draft_guide_ebauche_ld_scb-eng.pdf. Accessed 5 Apr 2013.
68. Malins A, Milne CP. Application of biopharmaceutics classification system in drug development. *Pharma Focus Asia*, Ochre Press. Issue 16. 2012. http://www.pharmafocusasia.com/research_development/application-Biopharmaceutics-Classification-System-Drug-Development.htm. Accessed 5 Apr 2013.