Mini-Review

BCS Biowaivers: Similarities and Differences Among EMA, FDA, and WHO Requirements

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Abstract. The Biopharmaceutics Classification System (BCS), based on aqueous solubility and intestinal permeability, has enjoyed wide use since 1995 as a mechanism for waiving *in vivo* bioavailability and bioequivalence studies. In 2000, the US-FDA was the first regulatory agency to publish guidance for industry describing how to meet criteria for requesting a waiver of *in vivo* bioavailability and bioequivalence studies for highly soluble, highly permeable (BCS Class I) drugs. Subsequently, the World Health Organization (WHO) and European Medicines Agency (EMA) published guidelines recommending how to obtain BCS biowaivers for BCS Class III drugs (high solubility, low permeability), in addition to Class I drugs. In 2015, the US-FDA became better harmonized with the EMA and WHO following publication of two guidances for industry outlining criteria for obtaining BCS biowaivers for both Class I and Class III drugs. A detailed review and comparison of the BCS Class I and Class III criteria currently recommended by the US-FDA, EMA, and WHO revealed good convergence of the three agencies with respect to BCS biowaiver criteria. The comparison also suggested that, by applying the most conservative of the three jurisdictional approaches, it should be possible for a sponsor to design the same set of BCS biowaiver studies in preparing a submission for worldwide filing to satisfy US, European, and emerging market regulators. It is hoped that the availability of BCS Class I and Class III biowaivers in multiple jurisdictions will encourage more sponsors to request waivers of *in vivo* bioavailability/bioequivalence testing using the BCS approach.

KEY WORDS: bioavailability; bioequivalence; biopharmaceutics classification system; *in vitro* dissolution; regulatory guidance.

INTRODUCTION

Ideally, access and affordability to medicines for all patients can be facilitated by global pharmaceutical development programs (1). As a result, simultaneous filings to multiple regulatory agencies are common within both the innovator and generic pharmaceutical industries (2). Although, in theory, simultaneous dossier submissions can greatly streamline the drug approval process, in practice, worldwide drug marketing approvals may be delayed due to region-specific regulatory requirements or dissimilar regulatory review outcomes from agencies of different jurisdictions. As per established published regulations, regulatory agencies are tasked with ensuring the quality, safety, and efficacy of all medications that they approve for marketing within their respective countries. Thus, designing a regulatory strategy that would meet the diverse needs of regulators worldwide is

a major challenge for drug developers who seek global markets.

One approach for which regulators have made great strides toward international harmonization is the application of the Biopharmaceutics Classification System (BCS). The BCS is an important tool for waiving the regulatory requirement for *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies in both new and generic drug development. This review will explain the BCS-based biowaiver process and its role in drug development, describe how the BCS biowaiver approach evolved from its inception to its present state, and summarize the current state of the BCS biowaiver implementation in several jurisdictions throughout the world.

Regulatory agencies have long recognized that, for some drug products, *in vivo* BA/BE may be self-evident and, as such, can waive the requirement for *in vivo* evidence (3) in certain circumstances (to grant a biowaiver). The use of biowaivers is in the spirit of avoiding unnecessary human testing whenever possible and facilitates access to drugs in jurisdictions such as the USA, EU, Canada, Australia, and also emerging countries. Application of the BCS in waiving BA/BE requirements is based on premises that if (1) two immediate-release (IR) drug formulations/products behave as oral solutions within the GI tract due to high solubility and rapid dissolution, (ii) no precipitation occurs in the GI tract once the API is dissolved, and (iii) the two IR formulations

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have the same *in vivo* dissolution profile under all intestinal luminal conditions, then they should have the same rate and extent of absorption, and therefore be bioequivalent (4). Another premise underlying the development of the BCS is the recognition that the two key factors governing drug absorption are aqueous solubility and intestinal permeability (5). Thus, the BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability (6). As such, the BCS designates all drugs as belonging to one of four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability) (5).

Ability to waive *in vivo* BE requirements using the BCS biowaiver approach can be pivotal to a successful regulatory submission, because demonstrating that two drug formulations/products are bioequivalent is an essential drug approval requirement for both innovator and generic drug products (7). Two drug formulations/products are deemed bioequivalent when they do not differ significantly in the rate and extent to which the active ingredient or active moiety becomes available at the site of action when the two formulations/products are given at the same molar dose under similar experimental conditions in an appropriately designed study (8–10). In generic drug development, demonstration of BE between the generic and its corresponding reference product is required for approval. In new drug development, BE is used to link the commercialized, to-be-marketed formulation and the clinical-scale formulation that underwent Phase III safety and efficacy testing. BE evidence is also required when commercialized drug products (whether new or generic) undergo certain types of scale-up or post-approval changes. Thus, in any of these regulatory situations where BE studies are deemed necessary for an IR solid oral dosage form, the potential exists for a BCS-based biowaiver, provided that the appropriate BCS designation criteria are met.

The first regulatory guidances encouraging the use of the BCS for biowaivers of Class I immediate-release (IR) solid oral dosage forms were issued by the US Food and Drug Administration (US-FDA) in 2000 (6, 11) and by the European Medicines Agency (EMA) in 2001 (12). Later, the World Health Organization (WHO) and EMA published guidelines allowing the granting of BCS biowaivers for both Class I and Class III drugs (9, 10). Initially, the WHO also considered granting biowaivers for some drugs of weak acids in Class II (13) but presently grants biowaivers for only Class I and Class III drugs. In May 2015, the US-FDA revised its BCS Guidance to expand the biowaiver provision to Class III drugs (14). Subsequently, in July 2015, the US-FDA posted a new draft Guidance for Industry which provided recommendations for *in vitro* dissolution testing and specification criteria for immediate-release solid oral dosage forms containing BCS Class I and Class III drugs (15). The EMA and US-FDA publish individual BE or product-specific guidances advocating the use of BCS biowaivers (16, 17), and the International Pharmaceutical Federation (FIP) has published 44 monographs on the subject (18). Presently, many emerging markets are implementing the BCS biowaiver approach based on jurisdiction-specific guidelines or the WHO guidelines.

Thus, the BCS is now widely established in the academic, industrial, and regulatory world for waiving the regulatory requirements of conducting comparative bioavailability studies to demonstrate *in vivo* BA/BE of immediate-release (IR) solid oral dosage forms containing BCS Class I and Class III drugs (5, 6). However, although great advances have been made recently in harmonizing some aspects of BCS biowaiver implementation among major regulatory jurisdictions, there remain a number of dissimilarities among them (notably, in Japan, the BCS biowaiver has not been implemented at all), presenting a challenge for innovator and generic companies that seek to utilize a BCS biowaiver approach for global registration of a drug product.

METHODS

The criteria, published in regulatory guidelines available in the public domain, which must be satisfied for consideration of granting a BCS-based biowaiver, for the US-FDA (14, 15), the EMA (9, 19), and the WHO (10), were compared. The selection of agencies for comparison is based on information presented at a Regulatory Sciences Open Forum (Proposals for Regulatory Harmonization of a Global BCS Framework – Challenges and Opportunities) during the 2014 American Association of Pharmaceutical Sciences (AAPS) Annual Meeting (13).

RESULTS

Table I compares the BCS biowaiver approaches currently used by the US-FDA, the EMA, and the WHO. The last column provides recommendations for what studies could be undertaken or what criteria/conditions to be met for a single regulatory filing that would satisfy the criteria of all three agencies.

DISCUSSION

With the posting of the Draft BCS Guidance in May 2015 and a Draft Dissolution Guidance in July 2015, the US-FDA moved into better convergence with the EMA and WHO with respect to the criteria necessary for granting a BCS-based biowaiver (the 2015 US-FDA Draft BCS Guidance replaced the original 2000 US-FDA BCS Guidance). Until the posting of the 2015 Draft BCS Guidance, the US-FDA would only grant biowaivers for Class I pharmaceutically equivalent IR oral dosage forms and would not consider biowaivers for Class III IR drug products. Notably, during the period from 2000 until 2015, to support granting a BCS biowaiver of a Class I drug, the US-FDA expected to see solubility determinations over the pH range of 1.0 to 7.5, considered *in vivo* evidence of high permeability to be *in vivo* $F_a \geq 90\%$, and would only accept *in vitro* dissolution testing via USP Apparatus 1 at 100 rpm or USP Apparatus 2 at 50 rpm (no exceptions). Aspects of the US-FDA BCS biowaiver approach until the 2015 posting of the Draft Guidance contrasted dramatically with the approaches of the EMA and WHO. Beginning in 2006 (WHO) and 2010 (EMA), both the EMA and WHO considered biowaivers for both Class I and Class III IR drug products (either pharmaceutical equivalents or alternatives), expected

Table 1. Similarities and Differences in Criteria for an Acceptable BCS-Based Biowaiver for the US-FDA, EMA, and WHO

Attribute/criteria	Parameter	US-FDA	EMA	WHO	Common positions
Type of BCS biowaiver considered by agency		I and III	I and III	I and III	I and III
Formulation comparison to reference or to risk	Type	<ul style="list-style-type: none"> - IR solid oral dosage forms; - Applicable to pharmaceutical equivalents; - May be applicable to pharmaceutical alternatives with justification 	<ul style="list-style-type: none"> - IR solid oral dosage forms; - Applicable to pharmaceutical equivalents or alternatives 	<ul style="list-style-type: none"> - IR solid oral dosage forms; - Applicable to pharmaceutical equivalents or alternatives 	<ul style="list-style-type: none"> - IR solid oral dosage forms; - Pharmaceutical equivalents or alternatives
	Excluded	<ul style="list-style-type: none"> - Any product designed to be absorbed in oral cavity (e.g., buccal or sublingual tablets); - Narrow therapeutic index drugs 	<ul style="list-style-type: none"> - Buccal, sublingual, and orodispersible formulations with absorption in oral cavity; - Narrow therapeutic index drugs 	<ul style="list-style-type: none"> - Orodispersible tablets are eligible if there is no sublingual or buccal absorption; - Narrow therapeutic index drugs 	<ul style="list-style-type: none"> - Any product designed to be absorbed in oral cavity; - Narrow therapeutic index drugs
	Acceptable excipients	<ul style="list-style-type: none"> - Class I: Usual excipients with quantity consistent with the intended function (e.g., lubricant); does not contain any excipients (e.g., surfactants and alcohol sugars like mannitol and sorbitol) that will affect the rate or extent of absorption of the drug; - Class II: Qualitatively the same and quantitatively very similar - Class III: Qualitatively the same and quantitatively very similar 	<ul style="list-style-type: none"> - Class I: Well-established excipients in usual amount; qualitatively and quantitatively the same for critical excipients (e.g., surfactants, mannitol, and sorbitol) should not differ qualitatively or quantitatively - Class III: Qualitatively the same and quantitatively very similar 	<ul style="list-style-type: none"> - Class I: Well-established excipients in usual amount; qualitatively and quantitatively the same for excipients that affect bioavailability - Class III: Composition must be qualitatively the same and quantitatively very similar 	<ul style="list-style-type: none"> - Class I: Well-established excipients in usual amount; qualitatively and quantitatively the same for excipients that affect bioavailability - Class III: Composition must be qualitatively the same and quantitatively very similar
	API	<ul style="list-style-type: none"> - Pharmaceutical alternatives not acceptable for ANDA; - For prodrug, site of conversion will determine whether permeability of prodrug or active drug should be determined 	<ul style="list-style-type: none"> - Not eligible if different ester, ether, isomer, mixture of isomer, complex, or derivative 	<ul style="list-style-type: none"> - Not discussed 	<ul style="list-style-type: none"> - Not accepted if different ester, ether, isomer, mixture of isomer, complex, or derivative; site of conversion for prodrug must be discussed
Solubility/high solubility conditions	pH	<ul style="list-style-type: none"> - Within 1 to 6.8. Base number of pH conditions on ionization characteristics of test drug substance to include pH = pKa; pH = pKa + 1; pH = pKa - 1, and at pH = 1 and 6.8 	<ul style="list-style-type: none"> - Within 1 to 6.8 (preferably at pH 1.2, 4.5, and 6.8 plus pKa if within 1–6.8) 	<ul style="list-style-type: none"> - Over the range of 1.2 to 6.8 	<ul style="list-style-type: none"> - Within 1 to 6.8; pH = pKa, pH = pKa + 1 and pKa - 1, and at pH 1 or 1.2, 4.5, and 6.8
	Method	Shake-flask or other justified method	Shake-flask or other justified method	Shake-flask or other justified method	Shake-flask or other justified method
	Volume	Soluble in 250 mL or less	Soluble in 250 mL	Soluble in 250 mL or less	Soluble in 250 mL or less
	temperature	37°C ± 1	37°C ± 1	37°C ± 1	37°C ± 1
	unit studied	Highest strength	Highest single therapeutic dose	Highest single therapeutic dose	Highest strength and highest single therapeutic dose
	timing of pH measure	After addition of the drug	Before and after addition of the drug	Not specified	Before and after addition of the drug
How to assess intestinal permeability	Origin of data	Sponsor	Sponsor	Not specified	Sponsor
	First choice	<ul style="list-style-type: none"> - High permeability if human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies; - <i>In vivo</i> intestinal perfusion studies in humans; 	<ul style="list-style-type: none"> - High permeability if human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies; 	<ul style="list-style-type: none"> - Human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies; - <i>In vivo</i> intestinal perfusion in humans is acceptable 	<ul style="list-style-type: none"> - For high permeability, human Fa ≥ 85%; - Human data preferred based on absolute BA or mass balance studies

Table I. (continued)

Attribute/criteria	Parameter	US-FDA	EMA	WHO	Common positions
Type of BCS biowaiver considered by agency		I and III	I and III	I and III	I and III
		<ul style="list-style-type: none"> - <i>In vivo</i> or <i>in situ</i> intestinal perfusion - Lack of degradation and studies in animals; - <i>In vitro</i> methods with epithelial metabolism in GIT must be monolayer cultures such as Caco-2 are ensured if BA data is derived acceptable only for passively absorbed mass-balance studies - Must show absence of dose dependency on Caco-2; - Limit the use of animal or <i>in vitro</i> permeability test methods for drug substances that are transported by passive mechanisms; - For permeability that is based on mass balance studies using total radioactivity, stability in GIT must be determined <i>in vitro</i> and discussed in relation with presystemic degradation 			
	Supportive	<ul style="list-style-type: none"> <i>In vivo</i> or <i>in vitro</i> permeability studies published in the scientific literature 	<ul style="list-style-type: none"> - <i>In vitro</i> permeability investigations; - Similar F between various formulations within the same route 	<ul style="list-style-type: none"> - <i>In vivo</i> or <i>in situ</i> perfusion in animal models; - <i>In vitro</i> permeation against a monolayer of intestinal cells - Similar F between various formulations within the same route 	<ul style="list-style-type: none"> - <i>In vivo</i> or <i>in situ</i> perfusion in animal models; - <i>In vitro</i> permeation against a monolayer of intestinal cells; - Similar F between various formulations within the same route
	Origin of data	Sponsor or in the labeling of the reference product; literature may be considered but always only in a supportive role	Sponsor or reliable source	Not specified	Sponsor or in the labeling of the reference product; literature may be considered but always only in a supportive role
Linearity of <i>in vivo</i> PK profile		Linear	Linear	Linear	Linear
Dissolution		Similarly rapid/very rapid	Similarly rapid/very rapid	Similarly rapid/very rapid	Similarly rapid/very rapid
- Criteria for fast and complete dissolution;	Rate of dissolution	Class I: $\geq 85\%$ 30 min	Class I: $\geq 85\%$ 30 min	Class I: $\geq 85\%$ 30 min	- If $\geq 85\%$ in 15 min, will support both Class I/III;
- Dissolution profile comparison	Extent dissolved	Class III: $\geq 85\%$ 15 min	Class III: $\geq 85\%$ 15 min	Class III: $\geq 85\%$ 15 min	- $\geq 85\%$ in 30 min, will support Class I only
	Maximum time				Basket at 100 rpm. Paddles at 50 rpm
	Apparatus	Basket (USP Apparatus I) at 100 rpm or paddles (USP Apparatus II) at 50 rpm or at 75 rpm when appropriately justified	Usually basket at 100 rpm or usually paddles at 50 rpm	Basket at 100 rpm or paddles at 75 rpm	
	Volume	500 mL	900 mL or less	900 mL or less	500 mL
	Media	3 pH (0.1 N HCl or Simulated Gastric Fluid without enzyme, 4.5, 6.8)	3 pH (0.1 N HCl or Simulated Gastric Fluid without enzyme, 4.5, 6.8)	3 pH (1.2, 4.5, 6.8)	3 pH (1.2, 4.5, 6.8)
		Surfactant discouraged	No surfactant	No surfactant	No surfactant
		No organic solvent	No surfactant	No surfactant	No organic solvent

Table I. (continued)

Attribute/criteria	Parameter	US-FDA	EMA	WHO	Common positions
Type of BCS biowaiver considered by agency		I and III	I and III	I and III	I and III
	Enzyme Unit tested	Yes in case of gelatin capsule shell Strength (1 dosage unit) for which BCS biowaiver is requested	No organic solvent Yes in case of gelatin capsule shell Strength (1 dosage unit) for which BCS biowaiver is requested	Yes in case of gelatin capsule shell Strength (1 dosage unit) for which BCS biowaiver is requested	Yes in case of gelatin capsule shell Strength (1 dosage unit) for which BCS biowaiver is requested
	No. of units	12	12	12	12
	Sampling times	Recommend 5, 10, 15, 20, 30 min	Recommend 10, 15, 20, 30, 45 min	Recommend 10, 15, 20, 30, 45 min	5, 10, 15, 20, 30, 45 min
	If $\geq 85\%$ in 15 min	No statistical test needed	No statistical test needed	No statistical test needed	No statistical test needed
	If $\geq 85\%$ dissolved in less than 30 min but longer than 15 min	F2 or other statistical test	F2 or other suitable test if conditions not fulfilled	F2 or equivalent statistical criterion	F2 or other suitable test if conditions not fulfilled
Number of batches		Not specified	Advise more than 1 of test and reference	Not specified	More than 1 of test and reference
Fixed dose combinations (FDC)		Both API's must comply	Both API's must comply	Waiver for only 1 component of a FDC is possible	Both API's must comply
Biowaivers of other strengths if 1 strength meets BCS biowaiver criteria		Not discussed	BCS-based biowaivers must be requested for all strengths	Not discussed	BCS-based biowaivers must be requested for all strengths

US-FDA US Food and Drug Administration, *EMA* European Medicines Agency, *WHO* World Health Organization, *ANDA* Abbreviated New Drug Application, *API* active pharmaceutical ingredient, *BCS* Biopharmaceutics Classification System, *IR* immediate-release, *BA* bioavailability, *GIT* gastrointestinal tract

solubility determinations over the pH range of 1.2 to 6.8, considered evidence of high permeability to be *in vivo* BA $\geq 85\%$, and would consider using paddle speeds of 75 rpm in rare (EMA) or all (WHO) circumstances. The low rate of BCS-biowaiver submissions from 2000 to 2015 may have been due in part to these differences (11); for example, from 2000 to 2015, the number of BCS biowaiver requests submitted to the US-FDA averaged approximately two per year (Mehta M. Applicability of BCS-Based Biowaiver: Requirements and Conditions – US-FDA Perspective. European Federation for Pharmaceutical Sciences Global Bioequivalence Harmonisation Initiative. Amsterdam, 2015).

Thus, the present BCS biowaiver approaches of the US-FDA, EMA, and WHO are in reasonably good agreement with respect to BCS Classes and IR dosage forms for which biowaivers are considered, definition of high *in vivo* permeability, and definition of highly soluble drug substance. There remain some notable differences among these three jurisdictions. With respect to establishing high solubility, the US-FDA appears to have the most stringent recommendations for which pH values to test. By contrast, the US-FDA asks that the highest strength be used for establishing high solubility, whereas the EMA and WHO ask that the highest therapeutic dose be used. With respect to establishing high permeability, the US-FDA will consider *in vivo* and *in situ* animal models and *in vitro* methods, such as those using cultured monolayers of animal or human epithelial cells—for passively absorbed drugs only—as pivotal methods, whereas the EMA and WHO consider these methods to be supportive only. With respect to establishing rapid or very rapid dissolution, the US-FDA now requests that dissolution testing use a volume of 500 mL, whereas the EMA and WHO request using the [typical] compendial volume of 900 mL or less.

In addition to posting its new draft guidance that recommends how to design solubility, permeability, and dissolution studies to establish that a drug is BCS Class I or III (14), the US-FDA also recently posted a draft guidance that provides recommendations on how to set dissolution specification criteria for IR Class I and Class III drug formulations (15). The two different draft guidances distinguish between dissolution testing to establish BCS Class *versus* dissolution testing that, together with chemistry, manufacturing, and controls (CMC) data, characterizes the quality and performance of the drug product to be marketed (20, 21). Thus, to establish BCS Class I or III, the US FDA presently recommends that applicants use the following: media of three pH values as noted in Table I; media volume of 500 mL: USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm or 75 rpm when justified; appropriate sampling times for dissolution profile generation; and statistical methods for comparing dissolution profiles.

By contrast, for stability and quality controls dissolution testing of Class I and III drugs, the US-FDA presently recommends that applicants use 500 mL of 0.01 M HCl aqueous media, USP Apparatus I at 100 rpm or USP Apparatus II at 75 rpm, a single point dissolution specification of $Q=80\%$ in 30 min for BCS Class I drugs, and a single point dissolution specification of $Q=80\%$ in 15 min for BCS Class III drugs. In addition, the US-FDA now recommends that, for drug products in both BCS Class I and III, USP

disintegration testing can be used in lieu of the dissolution test if the product is shown to meet a dissolution specification of $Q=80\%$ in 15 min.

CONCLUSION

The BCS is well established as a valid approach for waiving the requirements for *in vivo* BA and BE studies of Class I and Class III IR solid oral dosage forms in both new and generic drug development. The US-FDA, EMA, and WHO presently show good convergence with respect to the types of studies and documentation needed to establish that a drug is Class I or Class III. The US-FDA still differs somewhat from the other two jurisdictions with respect to criteria considered necessary to show high solubility, high permeability, and rapid dissolution, the latter to be performed in a smaller volume, 500 mL, compared to the EMA and WHO requirements which specify a volume of 900 mL. Nonetheless, these differences are such that, by applying the most conservative of the three jurisdictional approaches, it should be possible for a sponsor to design the same set of BCS biowaiver studies in preparing a submission for worldwide filing to satisfy US, European, and emerging market regulators.

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REFERENCES

1. Liberti L, Breckenridge A, Eichler HG, Peterson R, McAuslane N, Walker S. Expediting patients' access to medicines by improving the predictability of drug development and the regulatory approval process. *Clin Pharmacol Ther.* 2010;87:27–31. doi:10.1038/clpt.2009.179.
2. Handoo S, Arora V, Khera D, Nandi PK, Sahu SK. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. *Int J Pharm Investig.* 2012;2:99–105. doi:10.4103/2230-973X.104392.
3. US Food and Drug Administration. Title 21 code of federal regulations part 320 bioavailability and bioequivalence requirements. 2015. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=320>. Accessed 3 Dec 2015
4. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res.* 1995;12:413–20.
5. Chen ML, Amidon GL, Benet LZ, Lennernäs H, The YLX, BCS, BDDCS, and regulatory guidances. *Pharm Res.* 2011;28:1774–8. doi:10.1007/s11095-011-0438-1.
6. Shah VP, Amidon GL, Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res* 12, 413-420, 1995 – backstory of BCS. *AAPS J.* 2014;16:894–8. doi:10.1208/s12248-014-9620-9.
7. Amidon KS, Langguth P, Lennernäs H, Yu L, Amidon GL. Bioequivalence of oral products and the biopharmaceutics classification system: science, regulation, and public policy. *Clin Pharmacol Ther.* 2011;90:467–70. doi:10.1038/clpt.2011.109.
8. US Food and Drug Administration. Orange book: approved drug products with therapeutic equivalence evaluations. 2015.

- <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed 3 Dec 2015.
9. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP), guideline on the investigation of bioequivalence. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 3 Dec 2015.
 10. World Health Organization. WHO technical report series, No. 992 annex 7. Multisource (Generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. 2015. <http://apps.who.int/medicinedocs/documents/s21898en/s21898en.pdf>. Accessed 3 Dec 2015.
 11. Cook J. Impact of discordance among regulations for biopharmaceutics classification system based waivers of clinical bioequivalence studies. *Dissolution Technol.* 2015;22:6–10.
 12. European Medicines Agency. Guideline on the investigation of bioequivalence 20 Doc. Ref.: CPMP/EWP/QWP/1401/98 s.l.: Committee for Medicinal Products for Human Use (CHMP). 2001.
 13. Kanfer I. AAPS open forum report: proposals for regulatory harmonization of a global BCS framework: challenges and opportunities. *Dissolution Technol.* 2015;22:58–65.
 14. US Food and Drug Administration. Draft guidance for industry, waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. 2015. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>. Accessed 3 Dec 2015.
 15. US Food and Drug Administration. Draft guidance for industry, dissolution testing and specification criteria for immediate-release solid oral dosage forms containing BCS class 1 and class 3 drugs. 2015. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM456594.pdf>. Accessed 3 Dec 2015.
 16. European Medicines Agency. EMA/CHMP/736403/2014 Rev 2, compilation of individual product-specific guidance on demonstration of bioequivalence. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500189274.pdf. Accessed 3 Dec 2015.
 17. U.S. Food and Drug Administration. Guidance for industry, bioequivalence recommendations for specific products. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072872.pdf>. Accessed 3 Dec 2015.
 18. International Pharmaceutical Federation (FIP). Biowaiver monographs. 2015. http://www.fip.org/bcs_monographs. Accessed 3 Dec 2015.
 19. European Medicines Agency. EMA/618604/2008 Rev. 12, Questions and answers: positions on specific questions posted to the Pharmacokinetics Working Party (PKWP). 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf. Accessed 3 Dec 2015.
 20. U.S. Food and Drug Administration. Guidance for industry, dissolution testing of immediate release solid oral dosage forms. 1997. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070237.pdf>. Accessed 3 Dec 2015.
 21. United States Pharmacopeia. <1092> The dissolution procedure: development and validation. USP 36. Rockville: USP; 2015, p. 735.