



BIOPHARMACEUTICAL CLASSIFICATION SYSTEM: SCIENTIFIC BASIS FOR BIOWAIVER EXTENSIONS

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ABSTRACT

The Biopharmaceutical classification system (BCS) was introduced by Amidon *et al* in 1995 as a method to identify situations that might allow *in vitro* dissolution testing to be used to ensure bioequivalence in the absence of actual clinical bioequivalence studies of oral immediate release products with systemic actions. This approach is meant to reduce unnecessary *in vivo* bioequivalence studies however, is restricted to non-critical drug substances in terms of solubility, permeability, and therapeutic range, and to non-critical pharmaceutical forms. Although frequently discussed, BCS-based biowaivers are still rarely used probably attributed to uncertainties on both, pharmaceutical companies and regulatory authorities. Substantial differences of biowaiver dossiers and respective assessments contribute to the impression that a common understanding is lacking on a successful use of the BCS concept to support biowaivers

Keywords: Biopharmaceutical classification system (BCS), Bioequivalence, Solubility, Permeability, biowaivers.

INTRODUCTION

Biopharmaceutical Classification System (BCS) system allows restricting the prediction using the parameters solubility and intestinal permeability¹. The tenets of biopharmaceutics, solubility and permeability, are of pivotal importance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics on these two properties. The solubility classification is based on a United States Pharmacopoeia (USP) aperture². The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important, since 85% of the most sold drugs in the USA and Europe are orally administered. Ultimate aim of the drug discovery scientist in pharmacokinetic optimization is to tailor the molecules so that they show the features of BCS class I without compromising on pharmacodynamics. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal

permeability³. 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 immediate release (IR) solid oral dosage forms: dissolution, solubility, and intestinal permeability⁴. The biopharmaceutical classification system was developed primarily in the context of immediate release (IR) solid oral dosage forms. It was first introduced into regulatory decision-making process in the guidance document on Immediate Release Solid Oral Dosage Forms: Scale Up And Post Approval Changes. At first, biowaivers were only applied to Scale-Up and Postapproval Changes (SUPAC), but later the biowaiver principle was extended to the approval of new generic drug products. As a result, unnecessary human experiments can be avoided and the costs of developing generic products can be significantly lowered. According to the FDA guidance for the industry 'Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification

system' (August 2000), a biowaiver can currently be requested only for solid, orally administered immediate-release products (85% release in 30 min), containing drugs with a high solubility over the pH range from 1 to 7.5 (highest dose in 250ml media) and a high permeability (fraction absorbed 90%). In addition, only excipients which do not affect the rate or extent of absorption may be used. Further restrictions are that drugs with a narrow therapeutic range and drug products designed to be absorbed in the oral cavity may not be considered for biowaivers. A drug's solubility classification in the BCS is a function of the intended human dose. Drugs whose solubility under appropriate conditions exceeds the highest dose strength dissolved in 250 ml are classified as "soluble", i.e., Class I or III according to the BCS scheme. Drugs not meeting these criteria are classified as Class II or IV. Class I and Class II drugs have high permeability in an appropriate permeability assay system that has been validated with compounds of known *in vivo* human fractional absorption after oral administration. Drugs not meeting these criteria are class III, if they have high solubility, or class IV, if their solubility is low⁵.

Purpose of the BCS Guidance:

Expands the regulatory application of the BCS and recommends methods for classifying drugs. Explains when a waiver for *in vivo* bioavailability and bioequivalence studies may be requested based on the approach of BCS⁶. To improve the efficiency of drug development and the review process by recommending a strategy for identifying expendable clinical bioequivalence tests. To recommend a class of immediate-release (IR) solid oral dosage forms for

which bioequivalence may be assessed based on *in vitro* dissolution tests⁷. To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance.

Some important definitions

1. Absorption Number (A): It is the ratio of permeability (P) and the gut radius (R) times the residence time (T) in the small intestine, which can be written as the ratio of residence time and absorptive time (t).

2. Permeability: It is the ratio of rate of drug transport in receiver compartment (dM/dt) to the product of area of the membrane (A) and apical chamber drug concentration (C).

3. Dissolution Number (D): It is the ratio of the mean residence time (T) to the dissolution time (t), which includes solubility, diffusivity, density and the initial particle radius.

4. Bioavailability: The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

5. Bioequivalence: The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study

6. Biowaiver: A biowaiver³ is an exemption granted by the US FDA from conducting human bioequivalence studies when the active ingredient(s) meet certain solubility and permeability criteria *in vitro* and when the dissolution profile of the dose form

meets the requirements for an "immediate" release dose form.

7. Comparator product : Product containing similar amounts of the same excipients as the test product, sameness of the manufacturing method and quality of the test product. The difference in drug content or potency between the test and comparator products³ should be less than 5%.

8. Very rapidly dissolving product: At least 85 % of the labelled amount is released within 15 minutes or less from the test and the comparator product. In this case profile comparison is not needed.

9. Rapidly dissolving product: At least 85 % of the labelled amount is released within 30 minutes or less from the test and the comparator product. Profiles are superimposable or profile comparison test and the comparator product.

Criteria for BCS based biowaivers:

Biowaiver are based on the Biopharmaceutics (BCS) classification of the active ingredient. Currently BCS class I and some class III compounds are eligible for biowaivers.

- The drug substance should be highly soluble and highly permeable.
- An IR drug product should be rapidly dissolving⁸.
- The drug should not be a narrow therapeutic index drug.
- Excipients used in the dosage form should have been used previously in FDA approved IR solid dosage forms
- For waivers of an *in vivo* relative bioavailability study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media (acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer; and a pH 6.8

buffer or Simulated Intestinal Fluid USP without enzymes)⁹.

- For waivers of *in vivo* bioequivalence¹⁰, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products. Two dissolution profiles may be considered similar when compared using the f2 metric ($f_2 > 50$). When both the test and the reference products dissolve 85% or more of the label amount in < 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary.

BCS classes:

1. Class I - High Permeability, High Solubility

e.g. Metoprolol, Diltiazem, Verapamil, Propranolol

Class I drugs exhibit a high absorption number and a high dissolution number³. These compounds are generally very well absorbed. For those Class I compounds formulated as immediate release products, dissolution rate generally exceeds gastric emptying. Therefore, nearly 100% absorption can be expected if at least 85% of a product dissolves within 30 min of *in vitro* dissolution testing across a range of pH values. Accordingly, *in vivo* bioequivalence data are not necessary to assure product comparability.

2. Class II - High Permeability, Low Solubility

e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine

Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number³. The bioavailability of products containing these compounds is likely to be dissolution-rate limited. For this reason,

a correlation between in vivo bioavailability and in vitro dissolution rate (an IVIVC) may be observed.

3. Class III - Low Permeability, High Solubility

e.g. Cimetidine, Acyclovir, Neomycin B, Captopril

For Class III drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption³. Absorption is permeability-rate limited but dissolution will most likely occur very rapidly. For this reason, there has been some suggestion that as long as the test and reference formulations do not contain agents that can modify drug permeability or GI transit time, waiver criteria similar to those associated with Class I compounds may be appropriate.

4. Class IV - Low Permeability, Low Solubility e.g. taxol, hydrochlorothiazide, furosemide.

Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected³ with very poor oral bioavailability. These compounds are not only difficult to dissolve but once dissolved, often exhibit limited permeability across the GI mucosa. These drugs tend to be very difficult to formulate and can exhibit very large inter subject and intra subject variability.

Class boundaries:

1. Highly Soluble: A drug substance is considered highly soluble when the highest dose strength is soluble in ≤ 250 ml water over a pH range of 1 to 7.5⁹.

2. Highly Permeable: A drug substance is considered highly permeable when the extent of absorption in humans is determined to be $\geq 90\%$ of an administered dose, based on mass-balance or in

comparison to an intravenous reference dose³.

3. Rapidly Dissolving: A drug product is considered to be rapidly dissolving when $\geq 85\%$ of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of ≤ 900 ml buffer solutions³.

Determination of drugs solubility class:

The solubility class boundary⁵ is based on the highest dose strength of an IR product that is the subject of a biowaiver request. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water. An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at $37 \pm 1^\circ\text{C}$ in aqueous media with a pH in the range of 1-7.5. A sufficient number of pH conditions⁵ should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3-5, solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution

pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products. If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data.

Determination of permeability class:

Effective permeability (P) is generally described in terms of units of molecular movement distance per unit time (e.g. 10 cm/ s). High permeability drugs are those with an extent of absorption greater than or equal to 90% and are not associated with any documented instability in the gastrointestinal tract. These methods range from simple oil/water (O/W) partition coefficient to absolute bioavailability studies⁶.

a. Extent of absorption in humans:

- Mass-balance pharmacokinetic studies.
- Absolute bioavailability studies.

b. Intestinal permeability methods:

- *In vivo* intestinal perfusions studies in humans.
- *In vivo* or *in situ* intestinal perfusion studies in animals.
- *In vitro* permeation experiments with excised human or animal intestinal tissue.
- *In vitro* permeation experiments across epithelial cell monolayers¹¹.

Dissolution test methods:

In this guidance, an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using U.S. Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the media like 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, pH 4.5 buffer, pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes⁵.

Dissolution profile comparison:

Regulatory interest is to know how similar the two curves are, and for this reason, the f_2 comparison has been the focus in Agency Guidances. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time points results in a f_2 value of 50. FDA has set a public standard of f_2 value between 50-100 to indicate similarity between two dissolution profiles⁵. At least 12 units should be used for each profile determination. To use mean dissolution data, the % coefficient of variance at the earlier point should not be more than 20% and at other time points should not be more than 10%. The dissolution measurements of the two products (T and R, pre- and post- change, two strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same, e.g., for IR products 15, 30, 45 and 60 minutes, for ER products 1, 2, 3, 5 and 8 hours. Because f_2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product⁶. For products which are rapidly dissolving, i.e., more than 85% dissolution

Table 1: Table shows classification of orally administered drugs according to the BCS¹⁵

Drug	Solubility (mg/ml)	Permeability (*10 ⁻⁴ cm/sec)	Dose (mg)	BCS class
Atenolol	26.5	0.20	100	3
Carbamazepine	0.01	4.30	200	2
cimetidine	1.00	0.26	200	3
Furosemide	0.01	0.05	40	4
Hydrochlorthiazide	1.00	0.04	50	3
Propranolol	33	2.91	40	1
Verapamil	83	6.80	80	1

Table 2: Table shows Internal standards and efflux pump substrates:

Model drugs suggested for use in establishing suitability of a permeability method

Drug	Permeability class
Antipyrine	High (Potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (Potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (Potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (Potential IS candidate)
Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low (Zero permeability marker)
Ranitidine	Low

(Courtesy of WHO)

in 15 minutes or less, a profile comparison is not necessary. f_2 value of 50 or greater ensures sameness or equivalence of the two curves and, thus, the performance of two products. For circumstances where wide variability is observed, or a statistical evaluation of f_2 metric is desired, a bootstrap approach to calculate a confidence interval can be performed.

Additional considerations for requesting a biowaiver:

Excipients used in the dosage form must have been used in a previously

approved immediate release solid oral dosage form by the Food and Drug Administration³. The quantity of excipients in the IR product should be consistent with their intended function. Large quantities of certain excipients, such as surfactants (e.g., sodium lauryl sulfate) or osmotic ingredients (e.g., sorbitol) may be problematic. Conversion site of prodrug to drug must be considered, if it occurs before intestinal absorption then permeability study of drug must be done otherwise permeability study of prodrug must be done.

Exceptions for biowaiver application

Certain products are not applicable for application for waivers of bioavailability and bioequivalence study. Narrow Therapeutic Range Drugs such as digoxin, phenytoin are not considered for biowaiver application due to safety point of view. Products designed to be absorbed in the oral cavity like buccal tablets and lozenges are also not applicable for biowaiver application.

Applications of BCS:

Use of the BCS as a simple tool in early drug development to determine the rate-limiting step in the oral absorption process, which has facilitated the information between different experts involved in the overall drug development process. It can save both time and money—if the immediate - release, orally administered drug meets specific criteria, the FDA will grant a waiver for expensive and time-consuming bio-equivalence studies⁸. This step will certainly reduce timelines in the drug development process, both directly and indirectly, and reduce unnecessary drug exposure in healthy volunteers, which is normally the study population in BE studies. The application of a BCS strategy in drug development will lead to significant direct and indirect savings for pharmaceutical companies. BCS has been developed primarily for regulatory applications, but it has also several other applications in both the pre-clinical and clinical drug development processes and has gained wide recognition within the research-based industry. The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale-up and post approval changes in drug manufacturing⁷. BCS classification can therefore save pharmaceutical companies a significant amount in development time and reduce costs¹³.

Class I drugs: The major challenge in development of drug delivery system for class I drugs is to achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile. Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug.

Class II drugs: The systems that are developed for class II drugs are based on micronisation, lyophilization, addition of surfactants, formulation as emulsions and microemulsions systems, use of complexing agents like cyclodextrins.

Class III drugs: Class III drugs require the technologies that address to fundamental limitations of absolute or regional permeability. Peptides and proteins constitute the part of class III and the technologies handling such materials are on rise now days.

Class IV drugs: Class IV drugs present a major challenge for development of drug delivery system and the route of choice for administering such drugs is parenteral with the formulation containing solubility enhancers.

Conclusion:

BCS principles provide a reasonable approach for testing and approving drug product quality¹³. BCS applications for Class 2 and 3 are challenging, but at the same time provides opportunities for lowering regulatory burden with scientific rational¹⁴. BCS also provides an avenue to predict drug disposition, transport, absorption, elimination. The *in vivo* performance of the drug depends upon its solubility and permeability. The biopharmaceutical classification system is the guiding tool for the prediction of *in vivo* performance of the drug substance and development of drug delivery system to suit that performance.

REFERENCES

1. GL Amidon *et al.* A theoretical basis for a biopharmaceutical drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res* 1995; 12(3): 413-420.
2. USP 28-NF 23. 2005. The United States Pharmacopeia The National Formulary. Rockville MD. The United States Pharmacopeial Convention, Inc.
3. Guidance for Industry: Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System, FDA 2000.
4. CDER Guidance For Industry: Dissolution Tests of Immediate Release Solid Oral Dosage forms.
5. Kasim NA, Whitehouse M, Ramachandran C. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Mol Pharm* 2004; 1: 85-96.
6. The Biopharmaceutical classification system Guidance, Office of pharmaceutical science, US FDA, C.D.E.R.
7. General notes on Biopharmaceutical classification system – based biowaiver applications, WHO prequalification of Medicines Programme, Guidance document, April 2008.
8. Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: the central role of dose/solubility ratio. *Pharm. Res.* 2003; 20: 1917-25.
9. Yazdani M, Briggs K, Jankovsky C, Hawi A. The “high solubility” definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs. *Pharm. Res.* 2004; 21: 293-9.
10. Lipka E, Amidon G. Setting bioequivalence requirements for drug development based on preclinical data: optimizing oral drug delivery systems. *J Control Release.* 1999; 62: 41-9.
11. Artursson P, Palm K, Luthman K. Caco-2 monolayers in experimental and theoretical predictions of drug transport. *Adv. Drug Deliv. Rev.* 2001; 46: 27-43.
12. Gupta E *et al.* Review of global regulations concerning biowaivers for immediate release solid oral dosage forms. *Eur J Pharm Sci* 2006; 29: 315-24.
13. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Connor DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm Res* 2002; 19: 921.
14. Vogelpoel H, Welink J, Amidon GL, Shah VP. Biowaiver monographs for Immediate Release solid oral dosage forms based on Biopharmaceutics Classification System (BCS) literature data: Verapamil hydrochloride, Propranolol hydro-chloride, and Atenolol. *J Pharm Sci* 1993: 1945-56.
15. Lindenberg M, Kopp S, Jennifer B. Classification of orally administered drugs on WHO model list of essential medicines according to BCS. *Eur J Pharm* 2004; 58: 265-78.