Guidelines for

Bioequivalence Biowaiver

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INTRODUCTION

A Biowaiver means that *in vivo* bioavailability and/or bioequivalence studies may be waived (not considered necessary for product approval). Instead of conducting expensive and time consuming in vivo studies, **a dissolution test could be adopted as the surrogate basis for the decision** as to whether the two pharmaceutical products are equivalent.

The risk of therapeutic in equivalence of two immediate release products can never be reduced to zero, even if a full clinical study is performed. The conclusion of comparative clinical studies, *in vivo* bioequivalence studies, *in vitro* equivalence tests and biowaivers is based on statistics and scientific data that are assumed to be representative for the products at issue.

The aim of biowaiver guidance is to reduce the risk of bioequivalence to an acceptable level. Pharmaceutical development work aims at reducing the probability of manufacturing inequivalent formulations taking into account the critical aspects of the product at issue. In this context, the absorption phase is regarded as the critical process determining the equivalence of the pharmacokinetic profiles and thereby the therapeutic equivalence of the test and reference product.

In this report we will focus on BCS-based biowaivers. However, other type of biowaivers had been discussed in regulation.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

BCS categorizes APIs into four classes:

BCS class I	**HIGH** solubility and **HIGH** permeability
BCS class II	**LOW** solubility and **HIGH** permeability
BCS class III	**HIGH** solubility and **LOW** permeability
BCS class IV	**LOW** solubility and **LOW** permeability

REQUIREMENTS FOR A BCS-BASED BIOWAIVER

There have been certain requirements for a biowaiver study that include allowance of regulatory authorities like FDA and WHO etc. **The drugs should have high solubility and high permeability according to BCS.**

Requirements for a BCS-based biowaiver study include:

a- Dissolution Test in 3 different media (in 900 ml and at 37°C) which are:

Buffer pH 1.2, simulated gastric fluid without enzymes or 0.1N HCl.

Buffer pH 4.5.

Buffer pH 6.8 or simulated intestinal fluid without enzymes.

b- 12 samples in each media, paddle rotating at 50 rpm or basket at 100 rpm

c- Sampling times are 10, 15, 20, 30, 45 and 60 minutes.

d- The profiles of the test and reference products must be similar in all three media.

e- The products are similar if the similarity factor f2 ≥ 50 and both products show ≥ 85% dissolution in 15 min.

DATA TO SUPPORT REQUEST FOR A BIOWAIVER

The drug substance for which a waiver is being requested should be highly soluble and highly permeable.

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 7.5.
2. **Highly Permeable:** A drug substance is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
3. **Rapidly Dissolving:** 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 enzymes.

Quantities of data to support a request for biowaivers have to be submitted. Sponsors requesting biowaivers based on the BCS should submit the following information to the Agency for Review.

A. Data Supporting High Solubility

The following information should be included in the application:

a- A description of test methods including information on analytical method and composition of the buffer solutions.

b- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric or neutral) and dissociation constants (pKa).

c- Test results (mean, standard deviation and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml) and volume of media required to dissolve the highest dose strength.

d- A graphic representation of mean pH-solubility profile.

B. Data Supporting High Permeability

The following information should be included in the application:

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 studies.

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 monolayers.

The concept of permeability has been changed in European guidelines to absorbability and the criterion of highly absorbable is based exclusively on "human" absorption, determined **by means of mass balance studies or absolute bioavailability studies**, greater, or equal to 85% of the administered dose. **Data from animals or culture cells are only considered to be supportive**.

ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIO WAIVER

A. Excipients

BCS classification is related to API without excipients. However, literature evidence illustrates how excipients may affect the fraction of dose absorbed by modulating disintegration, solubilization or stabilizing a specific polymorphic form, thereby changing the dissolution characteristics of the API.

The effect of excipients is strictly limited by the guidance documents: qualitative differences in excipients from which an effect on the bioavailability could be expected are not accepted, whereas scientific reasoning may justify larger and still safe deviations.

Excipients used in the dosage form must have been used in a previously approved immediate release solid oral dosage form by the FDA.

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.

B. Prodrugs

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 BIO WAIVER APPLICATION

Certain products are not applicable for application for waivers of comparative bioavailability and bioequivalence study:

1- To reduce the severity of an incorrectly applied bio waiver, **narrow therapeutic index drugs** are excluded. However, the guidelines do not give a clear definition of a narrow therapeutic index drug, leaving room for individual discussion. According to the EMA, it is not possible to define a set of criteria to categorize drugs as narrow therapeutic index drugs and **it must be decided case by case.**

   Narrow Therapeutic Range Drugs such as digoxin, phenytoin is not considered for bio waiver application due to safety point of view.

2- Products designed to be **absorbed in the oral cavity** like buccal tablets and lozenges are also not applicable for bio waiver application.

SUMMARY OF BCS-BASED BIOWAIVER CONDITIONS

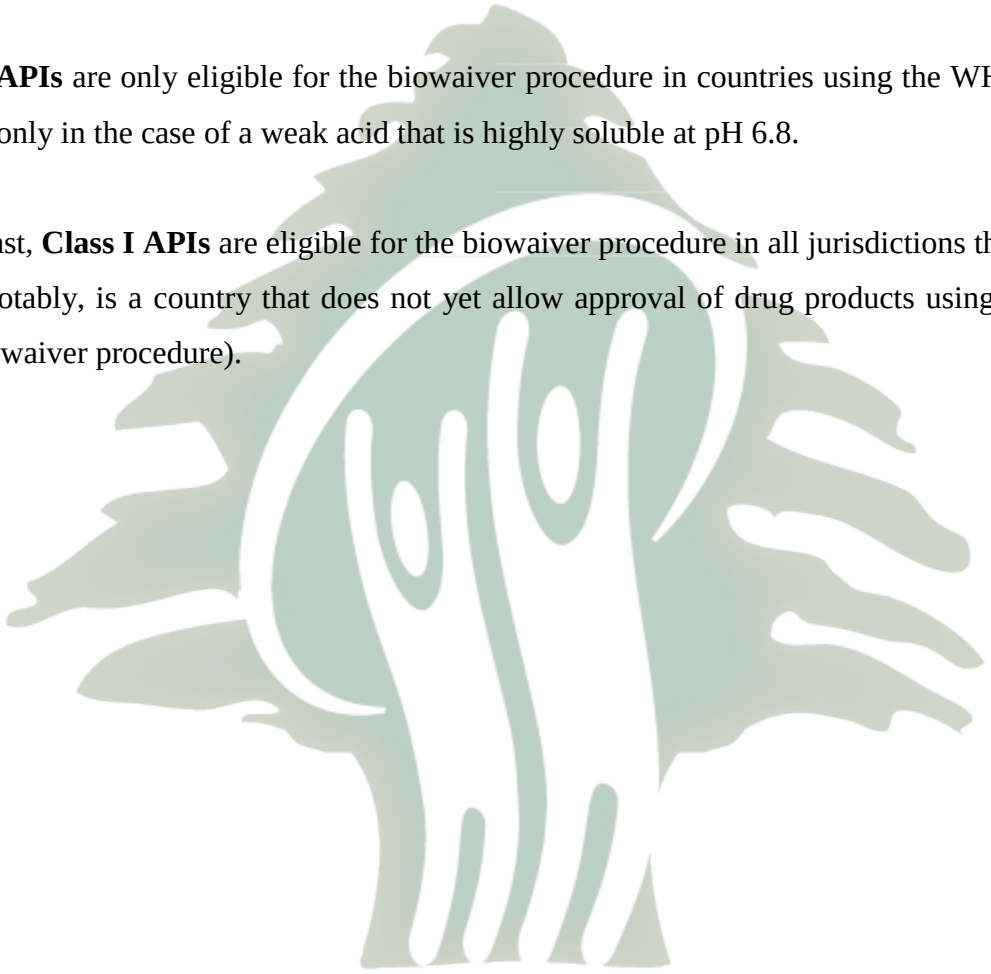
An important application of BCS in the regulatory documents is the use of BCS in the guidance for biowaiver procedures. One of the most important criteria for deciding whether a BCS-based biowaiver is appropriate is the BCS class of the API.

For instance, products containing BCS **class IV APIs are excluded** from the BCS-based biowaiver procedure.

Additionally, products containing **class III** APIs cannot, as of this writing, be approved in the USA by the biowaiver procedure. In the EU and countries using the WHO criteria, products containing Class III APIs are only eligible for biowaiving if they are very rapidly dissolving.

Class II APIs are only eligible for the biowaiver procedure in countries using the WHO criteria and then only in the case of a weak acid that is highly soluble at pH 6.8.

By contrast, **Class I APIs** are eligible for the biowaiver procedure in all jurisdictions that apply it (Japan, notably, is a country that does not yet allow approval of drug products using the BCS-based biowaiver procedure).



	EMA		FDA	WHO		
FORMULATION						
API	BCS class I	BCS class III	BCS class I	BCS class I	BCS class II	BCS class III
Excipients	excipients that might affect bioavailability are qualitatively the same	excipients that might affect bioavailability are qualitatively and quantitatively the same	excipients that are currently in FDA-approved IR solid oral dosage forms; not large quantities of certain excipients that might affect bioavailability	It should be demonstrated that the excipients … are well-established for use in products containing that API, and will not lead to differences with respect to processes affecting absorption, or which might lead to interactions that alter the pharmacokinetics of the API.		
Drug type	not for 'narrow therapeutic index (NTI)' drugs		not for NTI drugs and products designed to be absorbed in the oral cavity	Both the indication and therapeutic index are important considerations in determining whether the biowaiver based on BCS can be applied		
Dissolution formulation	very rapid (> 85 % within 15 min) or rapid dissolution (85 % within 30 min)	very rapid dissolution (> 85 % within 15 min)	rapid dissolution (NLT 85% in 30 min)	rapid dissolution: (NLT 85% in 30 min)	dose: solubility ratio of ≤ 250 ml at pH 6.8 and rapid dissolution: (NLT 85% in 30 min) in pH 6.8	very rapid dissolution (> 85 % within 15 min)
COMPARATIVE IN VITRO TEST						
In vitro dissolution testing	pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). No surfactant. Enzymes for gelatin only		pH 1.2, 4.5, and 6.8 or simulated gastric resp intestinal fluid. No surfactant. Enzymes for gelatin only	pH 1.2, 4.5, and 6.8		
EQUIVALENCE ACCEPTANCE CRITERIA						
	Similarity (f2 calculation 50-100) or other appropriate statistical method		Similarity (f2 calculation)	Similarity (f2 calculation 50-100) or other appropriate statistical method; provided that the same criterion is used for acceptance (maximum 10% difference between the profiles).		

LIST OF BCS-BASED BIOWAIVER ACCEPTED BY EMA (UP TO JANUARY 2015)

1. Almotriptan
2. Capecitabine
3. Levofloxacin
4. Lormetazepam
5. Memantine
6. Moxifloxacin
7. Temozolomide
8. Tramadol / Paracetamol

LIST OF CANDIDATES FOR BCS-BASED BIOWAIVER: INTERNATIONAL PHARMACEUTICAL FEDERATION (FIP) & JOURNAL OF PHARMACEUTICAL SCIENCE

The Special Interest Group (SIG) Biopharmaceutics Classification System and Biowaiver of the International Pharmaceutical Federation started to collect publicly available information for Essential Medical Drug Products based on the Biopharmaceutical Classification System.

This project takes published guidance of the WHO, FDA and EMA into consideration as well as scientific developments in this field. The collected information is critically reviewed and published as monographs in Journal of Pharmaceutical Sciences. They are also made available on the FIP Website (http://www.fip.org/www/index.php?page=bcs_monographs).

The list below has no formal regulatory status; it represents the best scientific opinion currently available. They are published in the Journal of Pharmaceutical Science but can also be downloaded on the link shown above.

1. Acetaminophen = Paracetamol
2. Acetazolamide
3. Acetylsalicylic acid

4. Aciclovir
5. Amitriptyline Hydrochloride
6. Amodiaquine Hydrochloride
7. Atenolol
8. Bisoprolol fumarate
9. Chloroquine Phosphate
10. Chloroquine Sulfate
11. Chloroquine Hydrochloride
12. Cimetidine
13. Ciprofloxacin Hydrochloride
14. Codeine phosphate
15. Diclofenac Potassium
16. Diclofenac Sodium
17. Doxycycline Hyclate
18. Efavirenz
19. Ethambutol Dihydrochloride
20. Fluconazole
21. Furosemide
22. Ibuprofen
23. Isoniazid
24. Ketoprofen
25. Lamivudine
26. Levetiracetam
27. Levofloxacin
28. Mefloquine Hydrochloride
29. Metoclopramide Hydrochloride
30. Metronidazole
31. Piroxicam
32. Prednisolone
33. Prednisone

34. Primaquine Diphosphate
35. Propranolol Hydrochloride
36. Pyrazinamide
37. Quinidine Sulfate
38. Quinine Sulfate
39. Ranitidine Hydrochloride
40. Rifampicin
41. Stavudine
42. Verapamil Hydrochloride
43. Zidovudine (Azidothymidine)

REFERENCES

Wagh MP, Patel JS. Biopharmaceutical classification system: Scientific basis for biowaver extensions. International Journal of Pharmacy and Pharmaceutical Sciences. **2010**; 2(1):12-19.

Benet LZ, Larregieu CA. The FDA should eliminate the ambiguities in the current BCS biowaiver guidance and make public the drugs for which BCS biowaivers have been granted. Clin Pharmacol Ther. **2010**;88(3):405-407.

Rohilla S, Rohilla A, Nanda A. Biowaivers: Criteria and Requirements. International Journal of Pharmaceutical & Biological Archives. **2012**;3(4):727-731.

García-Arieta A, Gordon J. Bioequivalence requirements in the European Union: critical discussion. AAPS J. **2012**;14(4):738-748.

Kubbinga M, Langguth P, Barends D. Risk analysis in bioequivalence and biowaiver decisions. Biopharm Drug Dispos. **2013**;34(5):254-261.

Sediq A, Kubbinga M, Langguth P, Dressman J. The impact of the EMA change in definition of "dose" on the BCS dose-solubility ratio: a review of the biowaiver monographs. J Pharm Sci. **2014**;103(1):65-70.

EMA, Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1/ Corr, London, 20 January **2010**

FDA, http://www.fda.gov/cder/guidance/index.htm

WHO, http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf

BCS Biowaivers Section - Bioequivalence Requirements in the European Union: Critical Discussion

This paragraph is copied from the reference:

García-Arieta A, Gordon J. Bioequivalence requirements in the European Union: critical discussion. AAPS J. **2012**;14(4):738-748.

The main advancement of the EU guideline in the area of BCS biowaivers is the acceptance of biowaivers not only for class I drugs, which was mentioned in the previous version, but also for class III drugs under strict conditions. Although there are several differences in approach compared with the US-FDA approach, like the US-FDA, narrow therapeutic index drugs are excluded and the biowaiver policy only applies to products with the same immediate release solid oral dosage forms (capsule *vs.* tablets is not acceptable, although this is allowed by the definition of generic medicinal products in Directive 2001/83). Similarly, in spite of the fact that different ester, ethers, isomers, mixtures of isomers, complexes, or derivatives of an active substance are considered to be the same active substance for the EU definition of generic medicinal product, only different salts of class I drugs are acceptable for biowaivers.

Although the guideline states that it only applies to products with systemic action, the same scientific principles could be applicable to gastrointestinal locally acting products (*e.g.,* acarbose). In contrast, it is not applicable to systemically acting products that are not absorbed in the gut (*e.g.,* sublingual and buccal) and orodispersible tablets since satisfactory dissolution methodology is not developed yet and, as explained above, the orodispersible tablets are usually taken without water, therefore, the definition of solubility based on 250 ml does not apply.

The classification as of a drug as highly soluble is based on the maximum single dose and not simply the maximum strength, the pH range of interest varies from 1 to 6.8 instead of 7.5, and the pH characterisation requirements do not include the p$K_a \pm 1$, but only pK_a.

The concept of permeability has been changed to absorbability and the criterion of highly absorbable is based exclusively on “human” absorption, determined by **means of mass balance**

studies or absolute bioavailability studies, greater, or equal to 85% of the administered dose. Data from animals or culture cells are only considered to be supportive. The data from the mass balance studies have to be interpreted in the light of the Biopharmaceutical Drug Disposition Classification System, taking into account that oxidative and conjugative metabolites are formed only systemically after absorption.

Although the EU guideline indicates that BE between a solid oral dosage form and an oral solution is supportive, as it is indicative that absorption limitations due to the dosage form are negligible, it does not signal that absorption is complete. In such situation, dissolution similarity is less relevant for class III drugs as BE between solid dosage forms and solutions is generally more easily accomplished for low permeability drugs than for extremely permeable drugs.

As per the EU guideline, dissolution profiles should be compared at pH 1.2, 4.5, 6.8, and the pH of minimum solubility in more than one batch of test and reference products. The agitation speed for these studies has been defined as usually 50 rpm for the paddle and 100 rpm for the basket apparatus. There is no guidance on when a different speed would be acceptable. A different agitation speed, *e.g.,* 75 rpm with the paddle apparatus as recommended by World Health Organization, is questionable since it would facilitate the demonstration of similarity.
Dissolution profiles must be similar and rapid (>85% in 30 min) for class I drugs, and similar and very rapid (>85% in 15 min) for class III drugs. Although rapid dissolution is less critical for some products containing class III drugs (perhaps not for those with an absorption window), the requirement of a very rapid release is to ensure that a solution is emptied from the stomach and therefore it can be considered as similar to oral solutions.

In the EU guideline, **special attention is paid to excipients** as excipients that may affect bioavailability have to be included in identical amounts in test and reference products. In contrast, the US-FDA asserts that large amount of surfactants or mannitol and sorbitol are necessary to alter bioavailability. However, experience in the EU has shown that small amounts of surfactants (*e.g.*, SLS) and sorbitol affect the bioavailability of drugs (*e.g.,* 4 mg of SLS

increases five- to six fold the bioavailability of alendronate, and 7 mg of sorbitol decreases the C_{max} of risperiodone with 60 mg also decreasing the AUC).

For class I drugs, excipients that are not known to affect bioavailability can be different but, for class III drugs, even these excipients have to be the same and in very similar amounts.