Biowaver presentation in the EU presented by the EU experts

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AIFA

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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Biowaiver

The biowaiver 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

Advantages:

- ❑ simplification of approval process
- ❑ reduction of development time and therefore overall product costs
- ❑ avoiding unnecessary human testing

Guidance on Biowaiver

- US Food and Drug Administration – 2017

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 Food and Drug Administration – 2015

Draft guidance for Industry - Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs.

Guidance on Biowaiver

- WHO – 2015

WHO technical report series, No.992 annex 7. Multisource (Generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.

- EMA – 2010

Guideline on the investigation of Bioequivalence
CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

Guidance on Biowaiver

Guideline on the investigation of Bioequivalence
CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

sets the relevant criteria under which bioavailability studies need not be required:

- ❑ waiver for additional strength
  (section 4.1.6)

- ❑ Biopharmaceutics Classification System (BCS) based Biowaiver
  (Appendix III)

Biowaiver

Different areas in which biowaver is applicable for:

- ❑ generic medicinal products
- ❑ line extensions (biowaivers of additional strengths)
- ❑ post approval changes (variations in formulation, excipients and or manufacturing process that require bioequivalence testing)
- ❑ formulation development (between early clinical trial products and to-be-marketed products)

Multiple strength biowaiver

- BCS independent

- If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths.

If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived.

Multiple strength biowaiver

General requirements to be met where a waiver for additional strength(s) is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process

b) the qualitative composition of the different strengths is the same

c) the composition of the strengths are quantitatively proportional [...]

d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing

In vitro dissolution tests for strength biowaiver

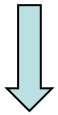
- Dissolution should be investigated at different pH values (pH 1.2, 4.5 e 6.8)

- Similarity of *in vitro* dissolution should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength used for bioequivalence testing

- A discussion is going on at CHMP to modify guidelines (surfactants, failed sink conditions)

Additional strengths biowaiver

Acceptability of an “additional strengths biowaiver” when bioequivalence to the reference product has been established with a BCS-based biowaiver



biowaiver of additional strength should be applied only when the test product have shown bioequivalence to the reference product by means of an in vivo bioequivalence study

Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP)
19 November 2015 EMA/618604/2008 Rev. 13
Committee for Human Medicinal Products (CHMP)

BCS-based Biowaiver

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

When combined with the dissolution of the drug product, BCS takes into account three key factors governing the rate and extent of absorption from IR solid oral dosage forms:

aqueous solubility
intestinal permeability
} drug substance

dissolution } drug product

BCS-based Biowaiver

Application of the BCS in waiving BA/BE requirements is based on premises that if

(i) two 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

(iii) the two IR formulations 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

Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivon bioavailability. Pharm Res. 1995;12:413–20

BCS-based Biowaiver

Four classes have been established as follows:

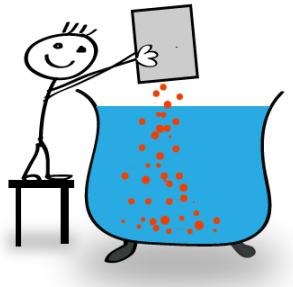
BCS class I HIGH solubility and HIGH permeability (HS/HP)

BCS class II LOW solubility and HIGH permeability (LS/HP)

BCS class III HIGH solubility and LOW permeability (HS/LP)

BCS class IV LOW solubility and LOW permeability (LS/LP)

BCS-based Biowaiver



Drug Substance – Solubility

The drug substance is considered highly soluble if

the highest single dose administered as immediate release formulation

is completely dissolved in 250 ml of buffers

within the range of pH 1 – 6.8 at 37±1 °C

Shake-flask method or other justified method should be used

BCS-based Biowaiver

Drug Substance – Permeability

The drug substance is considered highly permeable when the extent of absorption is ≥ 85 % of an administered dose

Complete drug absorption should be justified based on reliable investigations in human. Data from

- ☐ absolute bioavailability (comparison with intravenous dose)
- ☐ mass-balance

studies could be used to support this claim

BCS-based Biowaiver

Drug Product -In vitro Dissolution

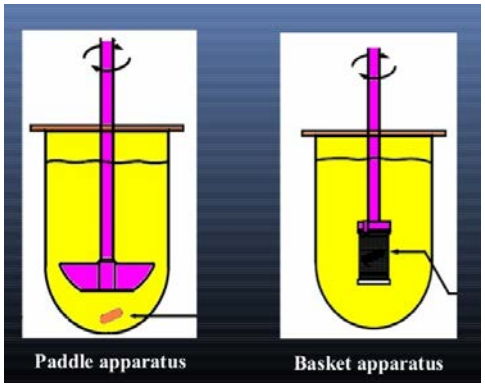
- Should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5 and 6.8)

- Additional investigations may be required at pH values in which the drug substance has minimum solubility

- The use of any surfactant is not acceptable. In case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable

BCS-based Biowaiver

Drug Product -In vitro Dissolution



Usual experimental conditions are:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation: paddle apparatus - usually 50 rpm
  basket apparatus - usually 100 rpm
- Sampling schedule:10, 15, 20, 30 and 45 min
- Buffer: pH1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes). Ph.Eur. Buffers recommended

BCS-based Biowaiver

Drug Product -In vitro Dissolution

- very rapidly dissolving: more than 85 % within 15 min
- rapidly dissolving: more than 85% within30 min
- slowly dissolving: more than 30 min for 85% dissolution

F2-testing or other suitable tests should be used to demonstrate profile similarity of test and reference.
An f2 value between 50 and 100 suggests that the two dissolution profiles are similar.

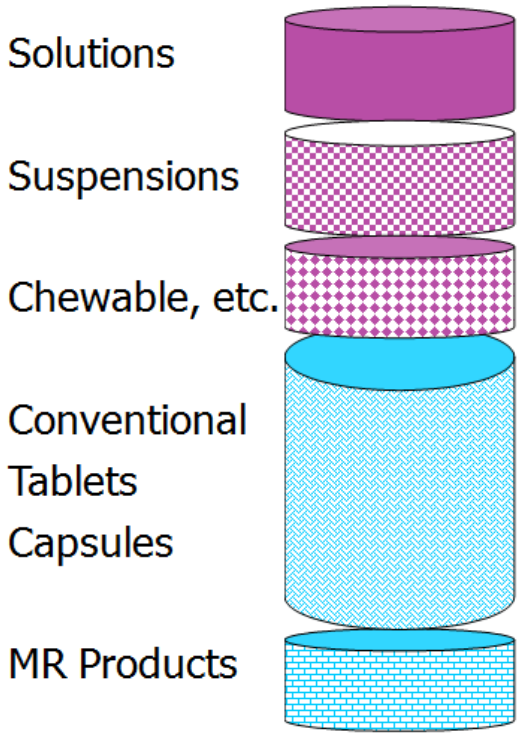
Dissolution tests: Debates

Dissolution tests are not sufficient to assure bioequivalence

Demonstration of IVIVC is necessary

IVIVC's are "Product Specific"

Differences in Drug Dissolution



"Self-evident" - Biowaiver possible
Condition- excipients do not alter absorption
(historical data)

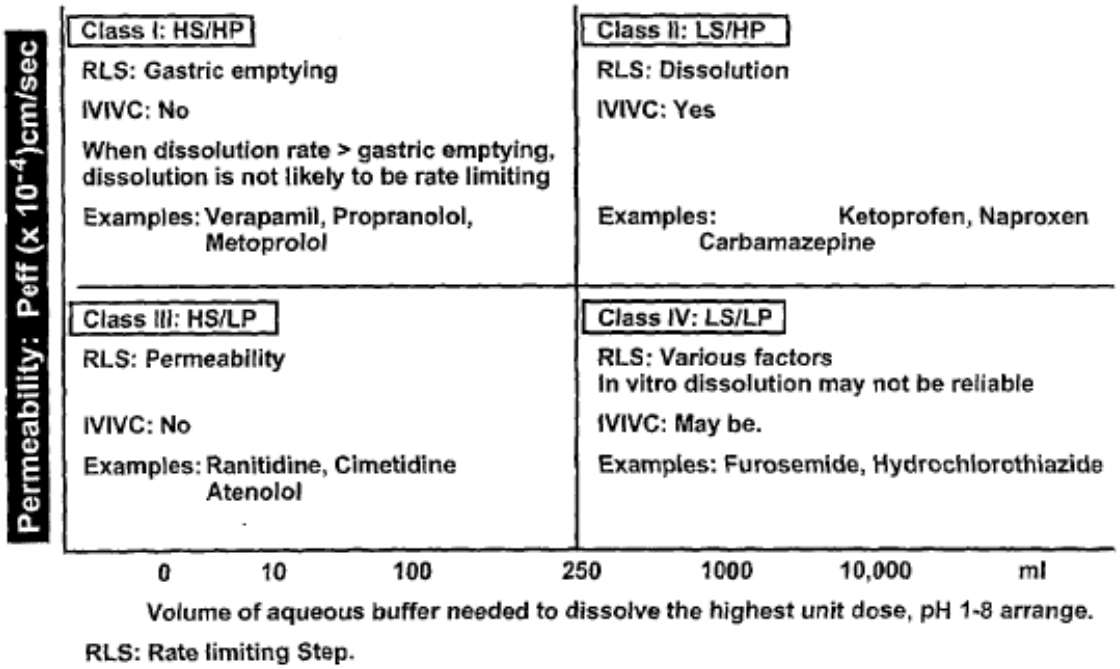
Pre-1962 DESI Drugs: *In Vivo* evaluation for "bio-problem" drugs (TI, PK, P-Chem)
Post-1962 Drugs: Generally *In Vivo* - some exceptions (IVIVC..)

SUPAC-IR (1995)
Dissolution-IR
Draft BCS
(pre-/post approval)

In VIVO

SUPAC-MR
IVIVC

BCS-based Biowaiver



RLS: Rate limiting Step.

BCS Class Boundaries: Objectives

Permeability

- High permeability ensure that drug is completely absorbed during the limited transit time through the small intestine

Solubility

- High solubility ensure that solubility is not likely to limit dissolution and, therefore, absorption

Dissolution

- Rapid dissolution ensure that in vivo dissolution is not likely to be the“rate determining” step

BCS-based Biowaiver

Additional parameters to be considered - Excipients

Excipients that might affect bioavailability (sorbitol, mannitol, sodium lauryl sulfate or other surfactants) should be identified as well as their possible impact on

- ☐ gastrointestinal motility
- ☐ susceptibility of interactions with the drug substance (e.g. complexation)
- ☐ drug permeability
- ☐ interaction with membrane transporters

BCS-based Biowaiver

Additional parameters to be considered - Excipients

- Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product

- It is advisable to use similar amounts of the same excipients in the composition of test like in the reference product

- If a biowaiver is applied for a BCS-class III drug substance excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters

BCS-based Biowaiver

Biowaiver may be applicable

- ❑ when the active substance in test and reference products are identical
- ❑ if test and reference contain different salts provided that both belong to BCS-class I
- ❑ to highly soluble drug substances with known human absorption
- ❑ to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form

BCS-based Biowaiver

Exclusion criteria from biowaiver :

- the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product

These differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept

- narrow therapeutic index drugs

BCS-based Biowaiver

Exclusion criteria from biowaiver:

- ❑ dosage forms intended for absorption in the oral cavity (sublingual or buccal tablets) and modified release formulations.
  For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded

- ❑ fixed-dose combination pharmaceutical product that contain an API where biowaiver is not applicable

BCS-based Biowaiver

BCS class I

- the drug substance has been proven to exhibit high solubility and complete absorption
- very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred

CPMP/EWP/QWP/1401/98 Rev. 1 (2010)

BCS-based Biowaiver

BCS class III

- the drug substance has been proven to exhibit high solubility and limited absorption
- very rapid (> 85 % within 15 min) in vitro dissolution of the test and reference product has been demonstrated considering specific requirements
- excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar

CPMP/EWP/QWP/1401/98 Rev. 1 (2010)

BCS-based Biowaiver

Generally the risks of an inappropriate biowaiver decision should be more critically reviewed
(e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks)
for products containing BCS class III than for BCS class I drug substances.

BCS-based Biowaiver

Product-specific bioequivalence guidance
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000625.jsp

BCS class II and IV→ in vivo studies are mandatory
BCS Class I and III→ the Applicant may choose between two options: in vivo approach or in vitro approach based on a BCS biowaiver.

The BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.).

BCS-based Biowaiver

However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

Biowaiver Monographs

Literature review:solubility, permeability, dissolution, bioequivalence data
– Review can suggest feasibility of biowaiver
– can also indicate when biowaiver is not recommended, e.g., ciprofloxaxin, furosemide, mefloquin
– Indicates criteria for in vitro equivalence test
– Examples include BCS Class 1, 2, 3. About 50 monographs are published

- No formal regulatory status, but represents the best scientific judgment
- Published in J Pharm Sci after peer review process
- Available on FIP web page http://www.fip.org/bcs_monographs

- API selected based on WHO list of essential drugs + other important drugs

BCS in the EU assessment practice

Strong support from scientific community

ACPS, Experts, FDA staff, Public workshops

Some concerns

"overly conservative"

very restrictive criteria

impact of excipients

poor interest in Class I drugs

fear of a medicine never administered to humans (swallowing, sticking, taste)

Conclusions

• BCS is used as a tool in product development to aid decision making and risk assessment

• BCS is a framework for identifying low-risk products based on solubility, intestinal permeability (absorption) and dissolution

• BCS applications for Class 2 and 3 are challenging, but at the same time provides opportunities for lowering regulatory burden with scientific rational

• BCS also provides an avenue to predict drug disposition (BDDCS) - transport, absorption, elimination

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