BCS-based biowaivers Industry perspective User View

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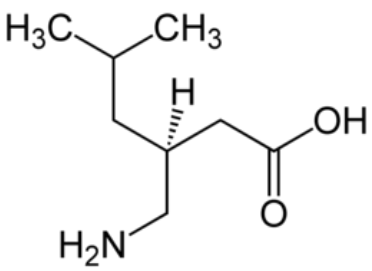
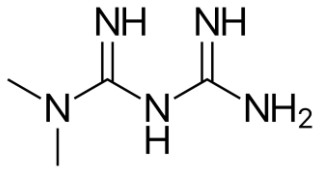
Sept 26-27th 2019, BioBridges, Prague

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

Pregabalin

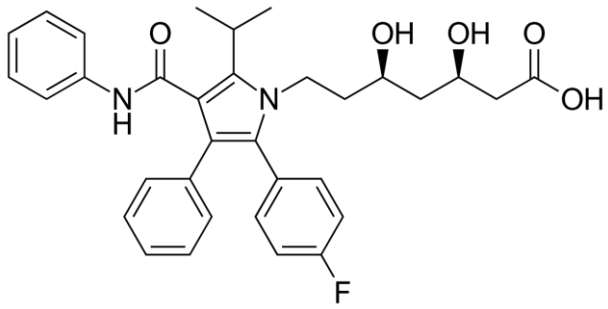


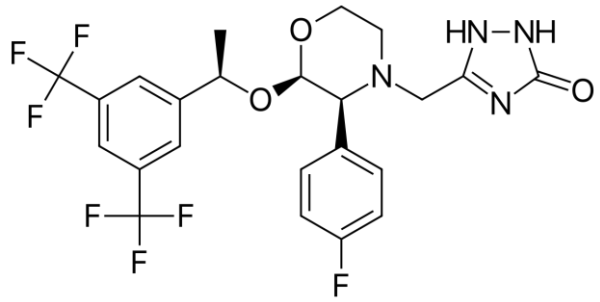
Metformin



permeability	solubility
	high solubility
	low solubility
high permeability	CLASS I
high permeability	CLASS II
low permeability	CLASS III
low permeability	CLASS IV

Atorvastatin





Aprepitant

Amidon, G.L., Lennernas, H., Shah, V.P. and Crison, J.R. (1995). A theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharmaceutical Research 12(3): 413-420

ICH M 9 draft: Comments

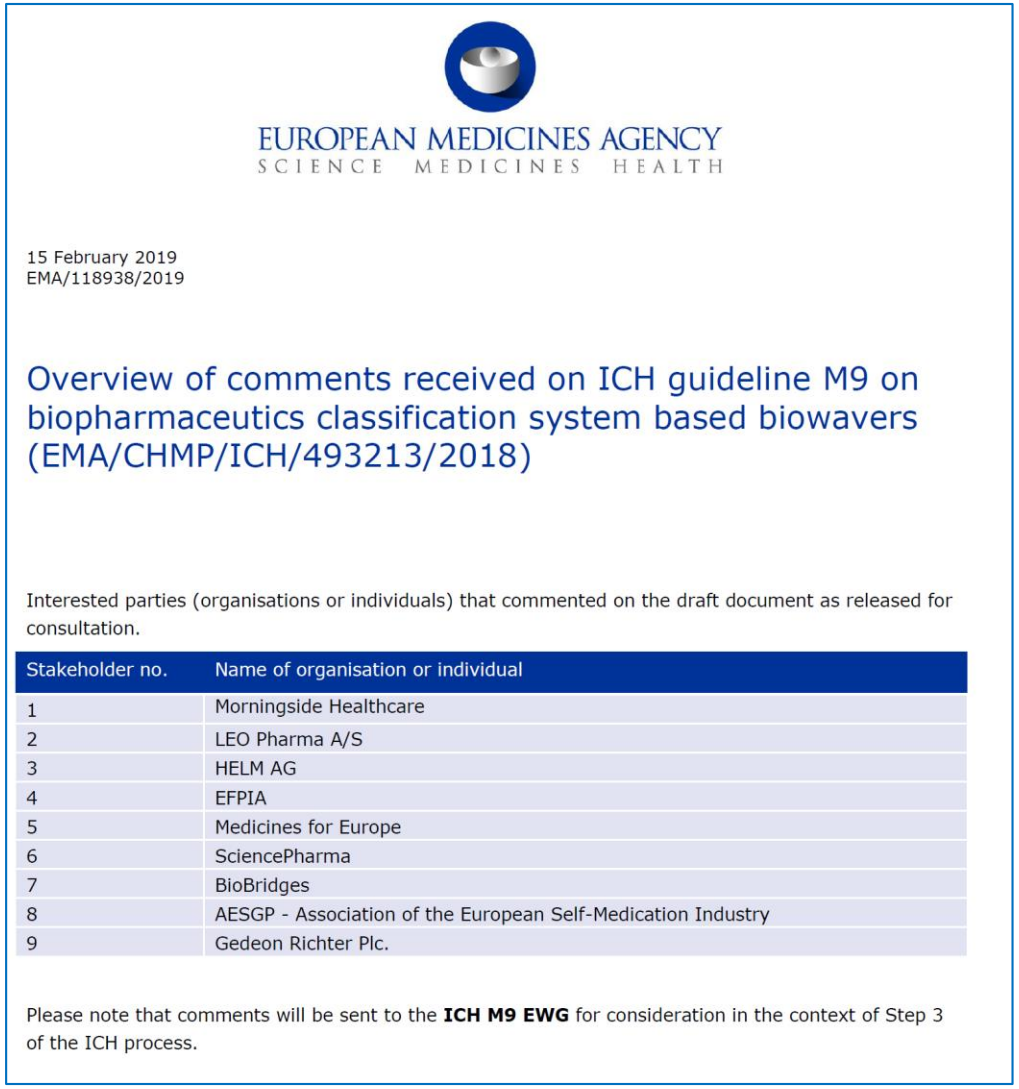
General comment:

"…approach not fully in line with the guideline should be supported when **convincing justification** provided."

Specific comments [lines]:

- **Different salts** not possible [67-68]
- **Moderate permeable compounds** (50–84%) regarded as poorly permeable

  [176-178]
- **Strictly set dissolution conditions** [197-203]
- BCS-based **strength** biowaiver [250-251]



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 February 2019
EMA/118938/2019

Overview of comments received on ICH guideline M9 on biopharmaceutics classification system based biowavers (EMA/CHMP/ICH/493213/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Morningside Healthcare
2	LEO Pharma A/S
3	HELM AG
4	EFPIA
5	Medicines for Europe
6	SciencePharma
7	BioBridges
8	AESGP - Association of the European Self-Medication Industry
9	Gedeon Richter Plc.

Please note that comments will be sent to the **ICH M9 EWG** for consideration in the context of Step 3 of the ICH process.

FINAL ENDORSED CONCEPT PAPER: Where the targets met?

Issues to be resolved

- Supportive data for **classification**

a) solubility

b) permeability

- Supportive data for a **waiver**

a) dissolution

b) excipients

Additional issues

- Different criteria for dissolution

- BCS-based strength biowaiver

ICH
harmonisation for better health

Final endorsed Concept Paper
M9: Biopharmaceutics Classification System-based Biowaivers
7 October 2016

Type of Harmonisation Action Proposed

This proposed new multidisciplinary guideline will address Biopharmaceutics Classification System (BCS)-based biowaivers. This guideline will provide recommendations to support the biopharmaceutics classification of medicinal products and will provide recommendations to support the waiver of bioequivalence studies.

This will result in the harmonisation of current regional guidelines/guidance and support streamlined global drug development.

Statement of the Perceived Problem:

Biopharmaceutics Classification System (BCS)-based biowaivers may be applicable to BCS Class I and III drugs, however BCS-based biowaivers for these two classes are not recognized worldwide. Regulatory guidelines/draft guidance which includes the possibility of BCS-based biowaivers have been issued in, for instance, the EU, US, Canada and within the WHO. Also, Japanese guideline includes the possibility of biowaivers based on the extent of formulation change. However, it appears from these guidelines that BCS based biowaivers may not be recognized globally or that the requested supportive data for such applications differs. In addition, even the classification itself may differ. This means that pharmaceutical companies have to follow different approaches in the different regions.

Points For Consideration

- Dose vs Strength
- Solubility methodology
- Degradation of API
- Comparator suitability
- BCS-based biowaivers in drug approvals
- Case studies

Bronze Age statue, 2000 BC

Solubility: Highest Single Dose versus Highest Strength

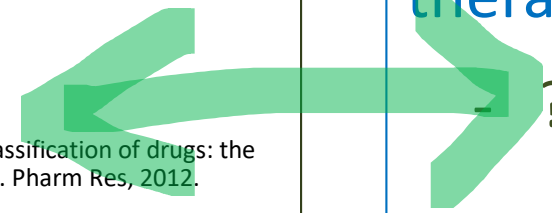
(Reality versus Theory or vice versa?)

BCS shift from I/III into II/IV

- verapamil, metoclopramide, …

Critical dose evaluation?

Charkoftaki, G., et al., Elucidating the role of dose in the biopharmaceutics classification of drugs: the concepts of critical dose, effective in vivo solubility, and dose-dependent BCS. Pharm Res, 2012.



Additional data

- dose proportional pharmacokinetics

(i.e. AUC and C_{max}) over a dose range that includes the highest therapeutic dose

- ? Anything else?

Solubility: Experimental conditions

- Equilibrium saturated solubility
- the check of pH and **adjustment** if necessary to ensure the specified pH
- **Validated** stability indicating method
- Degradation less than 10%

Degradation less than 10%: What is the relevant time frame?

- Over the extent of the solubility assessment – i.e. 24 hours?

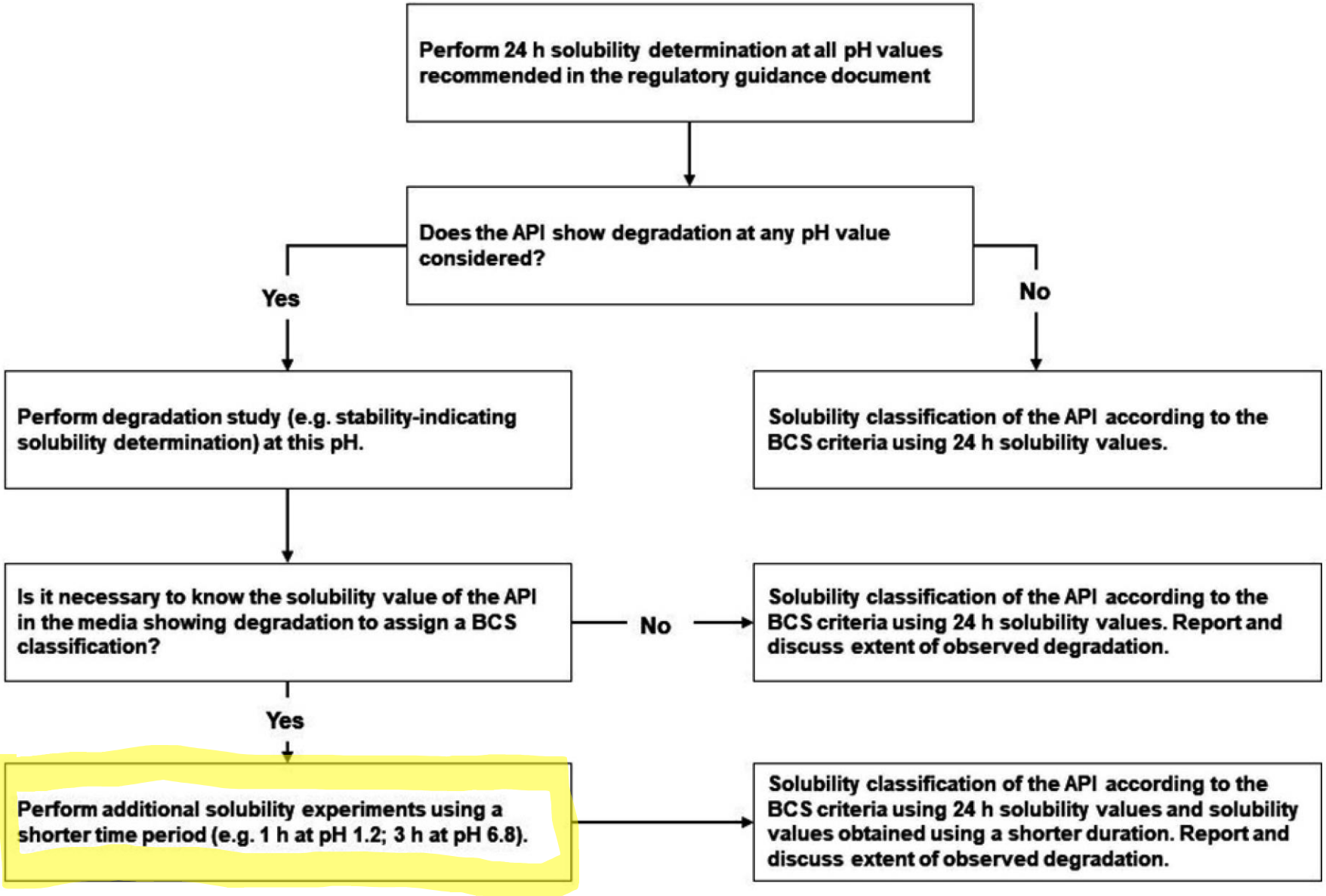
or

- Alignment with permeability specification? (i.e. 1 hour in gastric fluid + 3 hours in intestinal fluid)

Praxis:

- volume 250 mL…uneconomical for highly soluble APIs
- pH change reported but not adjusted consequently
- employment of UV spectral method with no capability of degradation observation

Dexamethasone: neutral molecule, highly soluble, no pH-dependency expected, however at pH 4.5, 2- and 3-foled higher solubility than at pH 1.2 and 6.8 observed

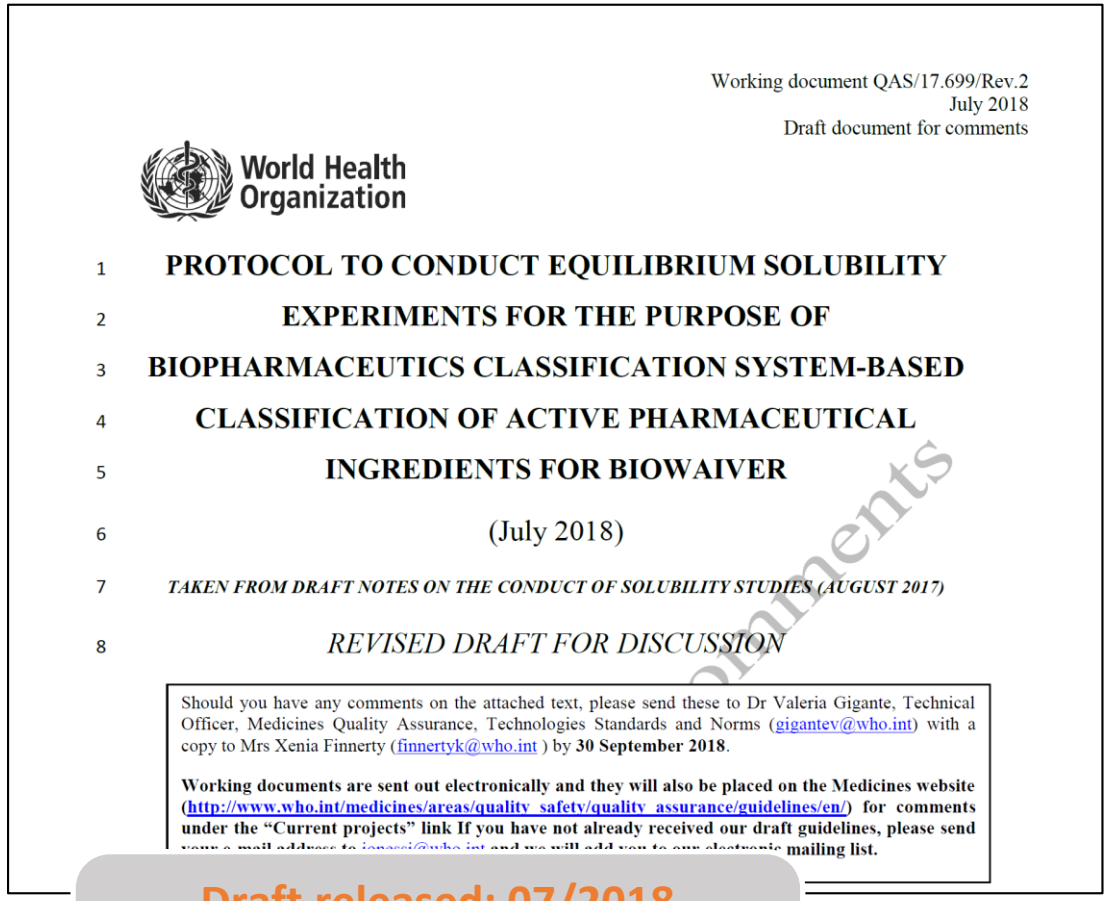


Ploger, G.F., M.A. Hofsass, and J.B. Dressman, Solubility Determination of Active Pharmaceutical Ingredients Which Have Been Recently Added to the List of Essential Medicines in the Context of the Biopharmaceutics Classification System-Biowaiver. J Pharm Sci, 2018.

Solubility: WHO Draft Protocol

Experimental design

- shake flask method,24 hours temperature, composition of buffers, three fixed pH
- Preliminary assessment (equilibrium & stability)
- Pivotal experiment
- Validated method to observe degradation
- Recommendation for the analytical method



Working document QAS/17.699/Rev.2
July 2018
Draft document for comments

World Health Organization

PROTOCOL TO CONDUCT EQUILIBRIUM SOLUBILITY EXPERIMENTS FOR THE PURPOSE OF BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED CLASSIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS FOR BIOWAIVER

(July 2018)

TAKEN FROM DRAFT NOTES ON THE CONDUCT OF SOLUBILITY STUDIES (AUGUST 2017)

REVISED DRAFT FOR DISCUSSION

Should you have any comments on the attached text, please send these to Dr Valeria Gigante, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (gigantev@who.int) with a copy to Mrs Xenia Finnerty (finnertyk@who.int) by **30 September 2018**.

Working documents are sent out electronically and they will also be placed on the Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "Current projects" link If you have not already received our draft guidelines, please send your e-mail address to ... and we will add you to our electronic mailing list.

Draft released: 07/2018

Deadline comments: 30/09/2018

Final: 2019-2020?

WHO: General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications (2019)

Active pharmaceutical ingredient (API)	Therapeutic group	Highest single dose [mg]	BCS Class
Abacavir (as sulfate)	Antiretroviral	600	III
Emtricitabine	Antiretroviral	200	I
Lamivudine	Antiretroviral	300	III
Stavudine	Antiretroviral	40	I
Zidovudine	Antiretroviral	300	I
Linezolid	Antibacterial	600	I
Fluconazole* (Polymorphs II & III)	Antifungal	800	I
Ethambutol	Anti-tuberculosis	400	III
Isoniazid	Anti-tuberculosis	300	III
Levofloxacin	Anti-tuberculosis	750	I
Moxifloxacin (as hydrochloride)	Anti-tuberculosis	400	I
Ofloxacin	Anti-tuberculosis	400	I
Pyrazinamide	Anti-tuberculosis	500	III
Diethylcarbamazine	Anti-parasitic	500	III**
Misoprostol (as 1% dispersion in HPMC)	Prostaglandin analogue	0.8	III**

….for products containing APIs for which PQTm has assigned a BCS classification…, a BCS-based biowaiver application can be made **without providing data for classification of the API**

WHO vs FDA vs EMA:
Is there a space for harmonized approach?

API	BCS class	FIP monograph (year)	Product specific guidance (BCS-based biowaiver option)	Alignment
Abacavir sulfate	III	Under preparation	FDA 2008 /not mentioned	
Emtricitabine	I	Under preparation	**FDA 2010 / eligible** **EMA / as FDC eligible**	✓
Lamivudine	III	2011	FDA 2008 / not mentioned	
Stavudine	I	2011	FDA 2008 / not mentioned	
Zidovudine	I	2013	FDA 2008 / not mentioned	
Fluconazol	I	2014	FDA 2018 / not mentioned	!
Ethambutol	III	2008	FDA 2017 / not mentioned	!
Isoniazid	III	2007	FDA 2008 /not mentioned	
Levofloxacin	I	2011	**FDA 2010 eligible**	✓
Moxifloxacin	I	---	---	
Ofloxacin	I	Under preparation	---	
Pyrazinamide	III	---	FDA draft 2016 / not mentioned	
Diethylcarbamazine	III	---	---	
Misoprostol	III	---	FDA 2010 / not mentioned	

COMPARATOR PROBLEM…

WHO: General Notes on BCS-based biowaivers applications

3. COMPARATOR PRODUCT SUITABILITY

Identification by PQTm of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, absorption, safety and related properties of the API (Class I or Class III). It does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of Class I APIs or very rapidly dissolving in the case of Class III APIs, which is a requirement for BCS-based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the PQTm website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving, or very rapidly dissolving, properties of a product are not required for *in vivo* bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.

- The need for internationally acknowledged comparator list:
  ☺ similar performance of generic medicines around the globe could be ensured

- ICH harmonized approach of BCS-based biowaivers?

Gwaza, L., et al., *Global Harmonization of Comparator Products for Bioequivalence Studies.* Aaps j, 2017.

BCS-based Biowaiver Role in Drug Approvals

EMA Product specific guidance permitting BCS-based biowaiver

BCS 1	BCS 3	Data to be generated
Agomelatine	Aliskiren	Entecavir
Emtricitabine	Tenofovir disoproxil	Imatinib (possible BCS 1)
Memantine	Sunitinib	Lenalidomide (possible BCS 1)
Paracetamol		Miglustat
Sitagliptin		Oseltamivir (possible BCS 3)
		Telithromycin

CASE STUDY: LENALIDOMIDE CAPSULES 25 MG

Lenalidomide hard gelatine capsules 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg product-specific bioequivalence guidance

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **Neither of the two** **Background:** Lenalidomide is a compound with complete absorption but the available data on solubility does not allow its BCS classification. If the applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, lenalidomide could be classified as BCS class I drug and a BCS biowaiver could be applicable.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 25 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics with limited information

+ FDA product specific guidance from 2013 does not mention the BCS-based biowaiver possibility

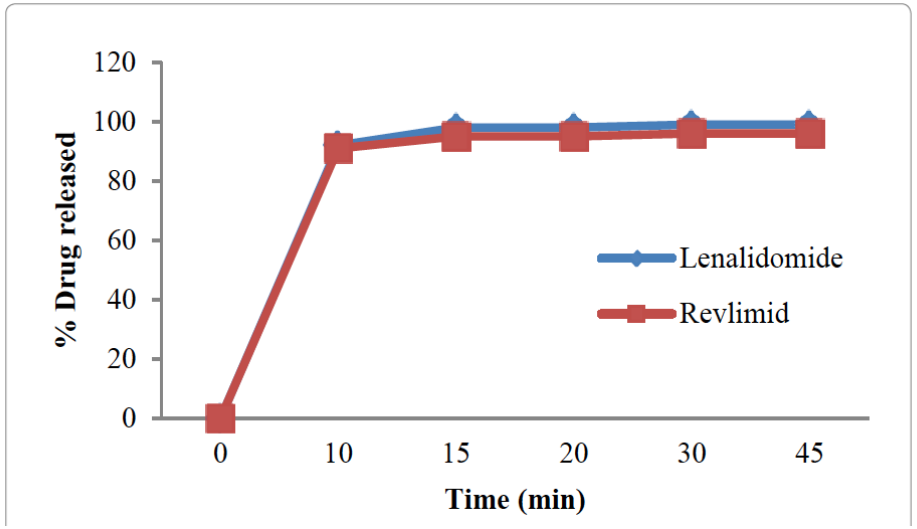
BCS class 1 demonstrated

D/S ratio 73.5 for pH 6.8

Absorption complete (<90% recovered unchanged in urine)

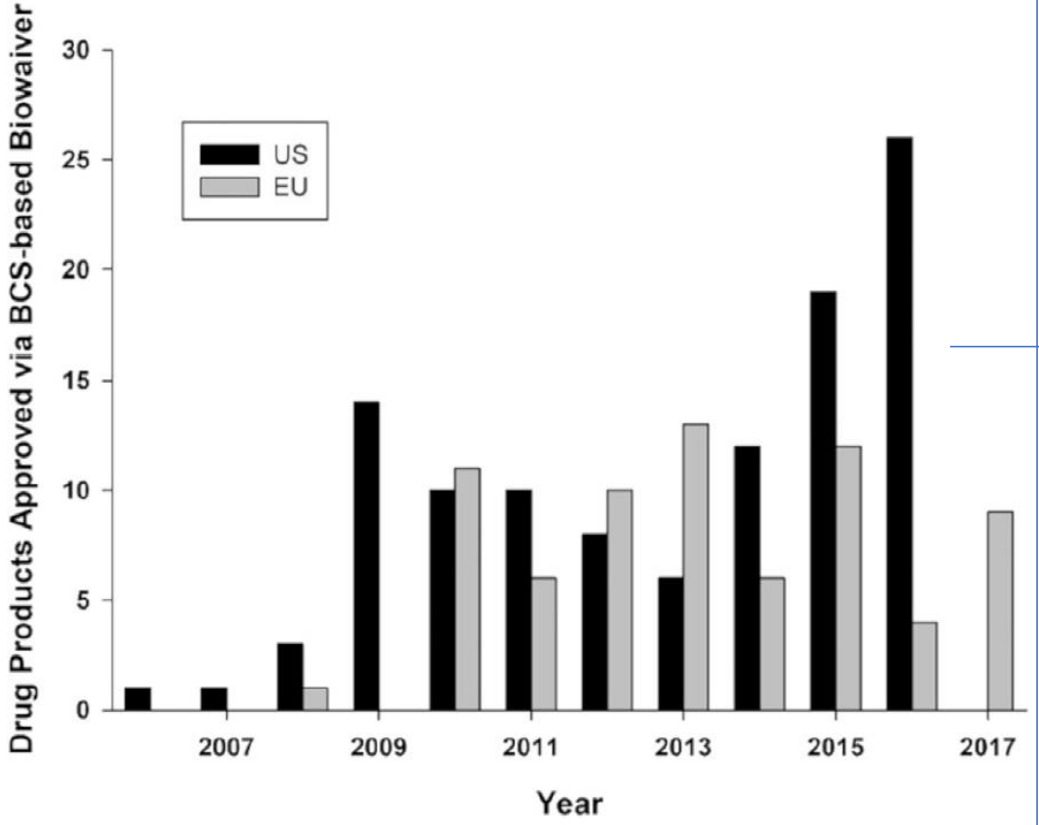
<85% dissolved in 15 min in all media

Excipients: qualitatively the same



Alswisi, M. et al., Biopharmaceutics Classification System Based Biowaiver Studies of Lenalidomide Capsules (25 mg) – An Alternative to In vivo Bioequivalence Studies for Generic Oncology Drug Products. Journal of Bioequivalence & Bioavailability, 2019

BCS-based Biowaiver Role in Drug Approvals – cont.



WHO

20th WHO Essential Medicines List

- Anti-infectives (41%)
- Oncology (13%)
- CNS (11%)
- Cardio-vascular (10%)

EU

EU Approved BCS-based Biowaivers

- CNS (48%)
- Analgetics (19%)
- Oncology (10%)
- Anti-Infectives (8%)

FDA

FDA approved BCS-based Biowaivers

- CNS (63%)
- Oncology (13%)
- Anti-Infectives (13%)
- Pulmonary/ GI (5%)

Hofsass, M.A. and J.B. Dressman, The Discriminatory Power of the BCS-Based Biowaiver: A Retrospective With Focus on Essential Medicines. J Pharm Sci, 2019.

CASE STUDY: PEDIATRIC ORAL SUSPENSION CONTAINING BCS CLASS 1 ANTIPYRETICS

ICH M9 draft guideline:

- BCS-based biowaiver applicable to immediate release, solid orally administered dosage forms or **suspensions** designed to deliver drug to the systemic circulation

- **Lacking**
  - Necessary adjustments to dissolution methods
  - Excipients variation

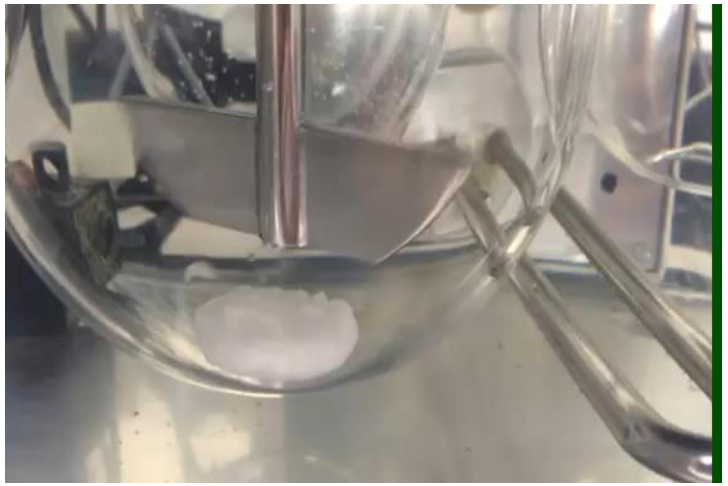
SmPC of the marketed "reference" products

- Posology 2.5–10 mL every 4 hours

or

- 10–20 mg/kg body weight

Reasonable sample size for comparative dissolution testing?



x FDA dissolution database

x USP monograph

CASE STUDY 1: cont.

EMA Product specific BE guidances general note to BCS-based biowaivers:

However, a BCS-based biowaiver might **not be feasible due to product specific characteristics** despite the drug substance being BCS class I or III…either for test or reference, or unacceptable differences in the excipient composition.

CASE STUDY 1: cont.

Ingredients	Qualitative Composition		Function
	Reference 1	Reference 2	
API	2.4 mg	2.4 mg	Active ingredient
Excipients			
Sorbitol	√	√	Sweetener
Sorbitol liquid	√	√	Sweetener
Maltitol liquid	√	√	Sweetener
Xanthan gum	√	√	Thickener, suspending agent
Citric acid	√	√	pH modifier
Malic acid	√	√	pH modifier
Flavour	√	√	Flavour
Colorant	√	√	Colorant
NIPASEPT	√	√	Preservative
Water qs to	100	100	Vehicle

Composition of the reference products
(Different market and MAH)

Physicochemical properties of TEST

- pH comparable
- density comparable
- viscosity comparable

Design of dissolution comparability testing

- 3 pH, paddle, 50 rpm
- criteria > 85% in 30 min

CASE STUDY 1: cont.

Results of dissolution testing at 50 rpm with the reference product

1. Great batch to batch variability
2. Sample not dispersed in the medium
3. Less than 85% in 30 min
4. Sample volume dependent rate of dissolution

So is there a space for dissolution method development with appropriate justification?

1. Higher rotation speed
2. Sample introduction to ensure dispersion of the product
3. Sample volume determination (considering that the highest single dose is 12.5 mL)

197-203	7	**Comment:** In the draft ICH guideline, the conditions for dissolution testing particularly the rotation speed (i.e. paddles 50 rpm, basket 100 rpm), are strictly set. In the current EMA bioequivalence guideline where only "usual" experimental conditions are defined there is a possibility for justification when the conditions used are different. For example, in some cases of oral suspensions containing BCS class I substances, rapid dissolution cannot be obtained under conditions prescribed by the draft (i.e. paddles 50 rpm) for the test as well as for the reference due to the high viscosity of the formulation. The case-by-case approach should be justifiable when assessing the suitability of dissolution conditions for BCS-based biowaivers. **Proposed change:** The following conditions should be employed (unless otherwise justified) in the comparative dissolution studies to characterize the….

CASE STUDY 2: BCS 1 Cardioselective Beta-Blocker

Indications as per SmPC (reference product)

- Hypertension
- Ischemic heart disease (angina pectoris)
- Stable chronic heart failure with decreased systolic function of left ventricle; concomitant therapy with ACE inhibitors, diuretics and eventually with heart glycosides.

- **Strengths: 10/ 5/ 2.5 mg**

- **Composition:**

not dose-proportional (amount of filler changed in account for the active substance)
= mass equivalent

- **film-coated tbl versus conventional**

Excipient	Product	
	Reference	Test
Cellulose microcrystalline	+	Similar qualitative composition
Silica, colloidal anhydrous	+	
Maize starch	+	
Crospovidone	+	
Magnesium stearate	+	
Calcium hydrogen phosphate, anhydrous	+	

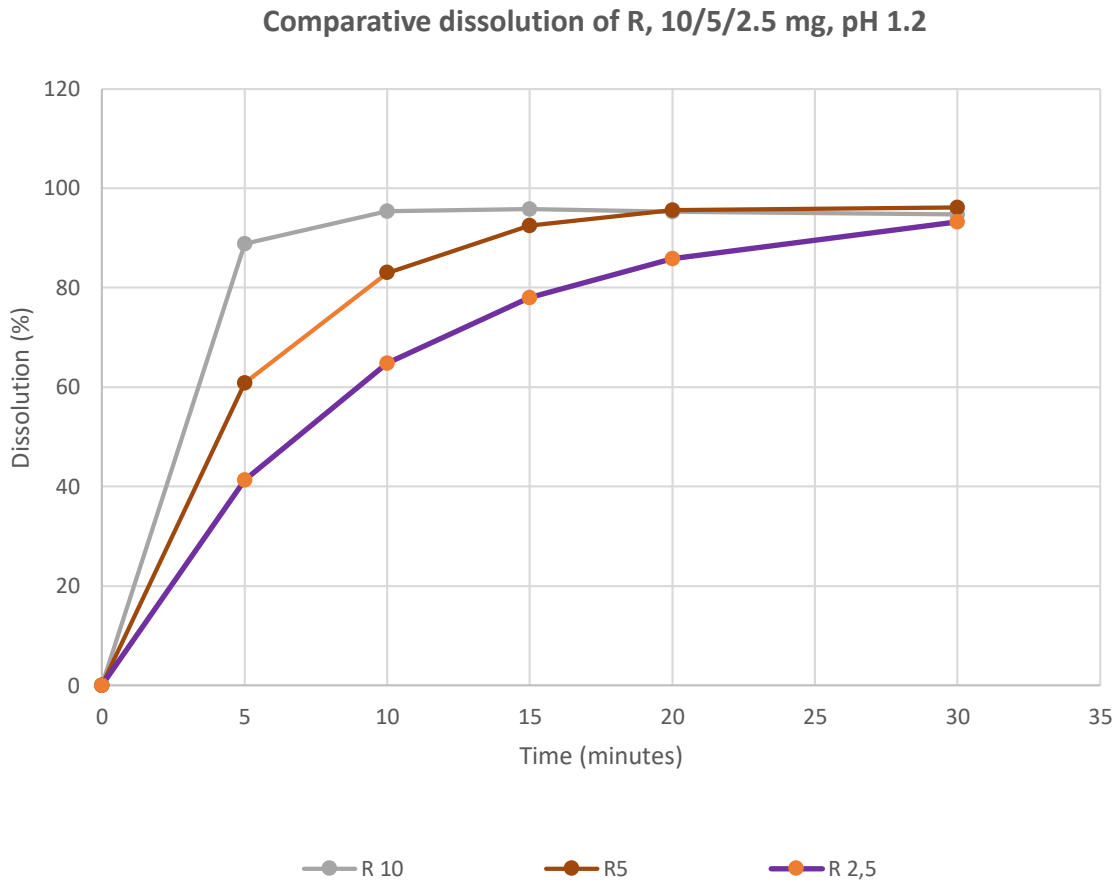
CASE STUDY 2: cont.

Strength	Dissolution results (pH 1.2, 4.5, 6.8)	Conclusion on similarity (T x R)
	REFERENCE	
10 mg	> 85% in 15 min	similar
5 mg	> 85% in 15 min	similar
2.5 mg	> 85% in 30 min	F2 = 31

test	medium	comparator	f2
R 2.5 mg	0.1 M HCl	R 5 mg	47.5
		R 10 mg	31.2
	pH 4.5	R 5 mg	49.8
		R 10 mg	36.7
	pH 6.8	R 5 mg	42.8
		R 10 mg	33.9

similarity could not be demonstrated across the strengths of the reference product!!

Dissolution conditions: 900 mL, 100 rpm, baskets, 12 units tested



CASE STUDY 2: cont.

The proposed approach: Testing at the same dose

2.5 mg T versus ½ 5 mg R

2x2.5 mg T versus 5 mg R

CASE STUDY 3: Metoprolol tartrate

European reference product: Seloken 100 mg

- lower strengths unavailable
- options for the authorization of lower strengths if similarity based on the stregth-biowaiver cannot be demonstrated?

Metoprolol:

- Highly permeable compound
- Absorption > 95%
- t_{max} 1.5–2 h
- BE demonstrated for tablets with different release characterictics
- dissolution not the rate-limiting
- range of dissolution profiles can be expected to yield **equivalent plasma profiles**

Polli et al. (1997) Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. J.Pharm. Sci.

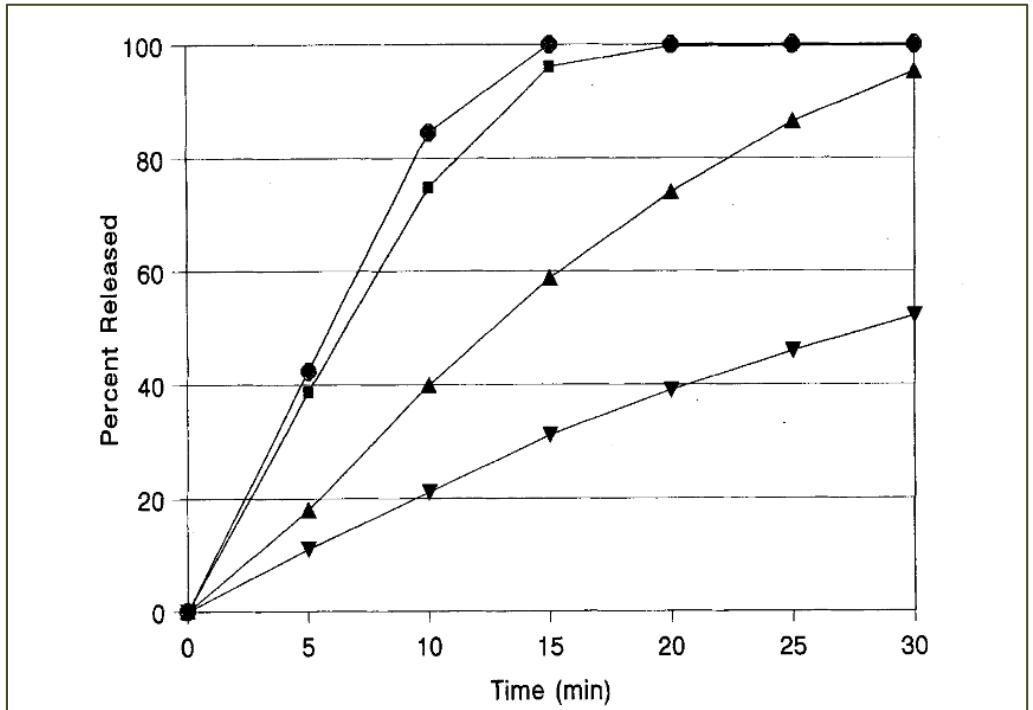


Figure 1. Mean dissolution profiles for metoprolol tartrate tablets used in biostudy.

CASE STUDY 3: cont.

The extension of guidance criteria for certain compounds?

Polli et al. (1997): Dissolution specification for metoprolol tartrate may be widened to “complete release in 60–90 min” and still assure BE

In Conclusion…

Keeping the rules is not comfortable in every situation!

Let’s make finding the new ways possible…

Acknowledgements:

Dr. Vít Perlík

Dr. Jiří Hofmann

Thank You For Your Attention