BCS-Based Biowaivers: Which Drugs are Eligible?

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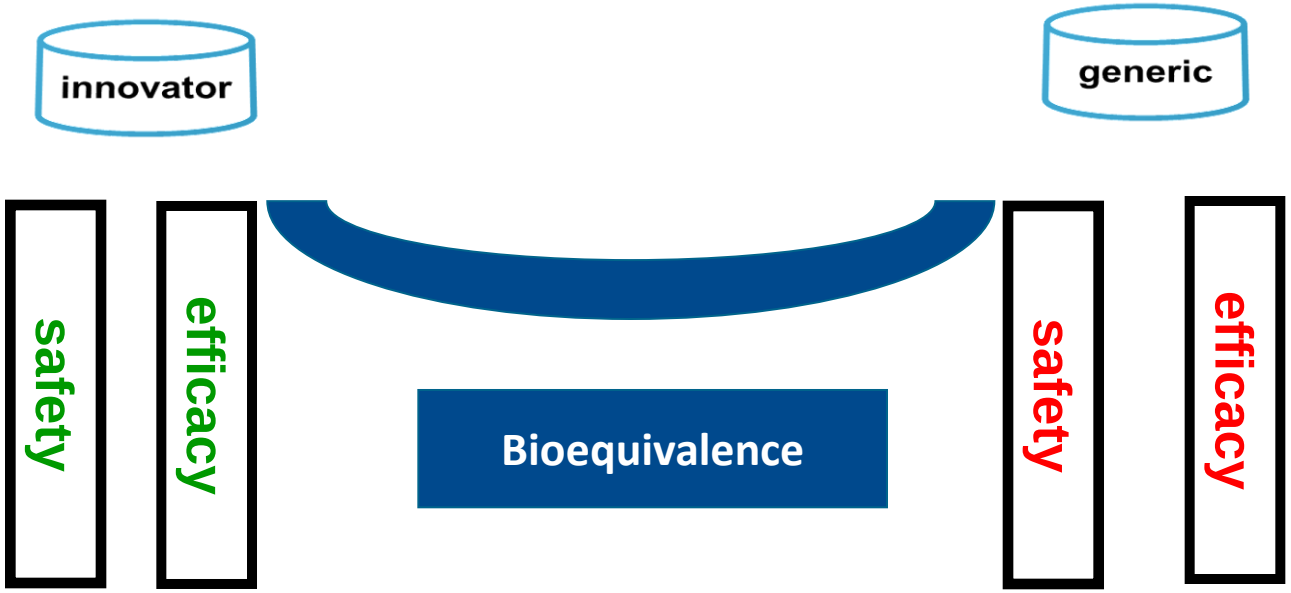
Scope

- Biowaiver concept
- Application of the biowaiver procedure as a surrogate for bioequivalence testing

What is bioequivalence?



Therapeutic equivalence = Pharmaceutical equivalence + Bioequivalence

Bioequivalence study

Situations where regulatory authorities have to decide whether bioequivalence study is mandatory or not

- *within the product*
  - Scale up processes or variations after marketing authorization (Scale up and Post Approval Changes –US FDA and Variations- EMA)
  - Approval of lower dose products

- *with another product*
  - Approval of generics without clinical data

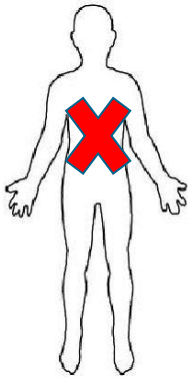
Bioequivalence study

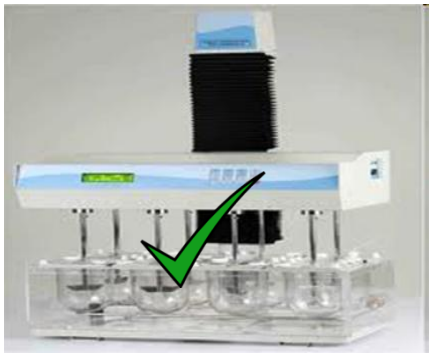
Bioequivalence between the comparator and the test products can be demonstrated by any one of the following techniques

- Pharmacokinetic studies
- Pharmacodynamic studies (e.g. topical products for local use)
- Clinical trials
- Biowaiver procedure (based on BCS classification)

What is a Biowaiver?

"Biowaiver" means avoiding time consuming and costly pharmacokinetic studies and using *in vitro* dissolution test as a surrogate test to evaluate the bioequivalence of a test and reference product





Advantages

•Circumvent expensive and sometimes unethically questionable human testing

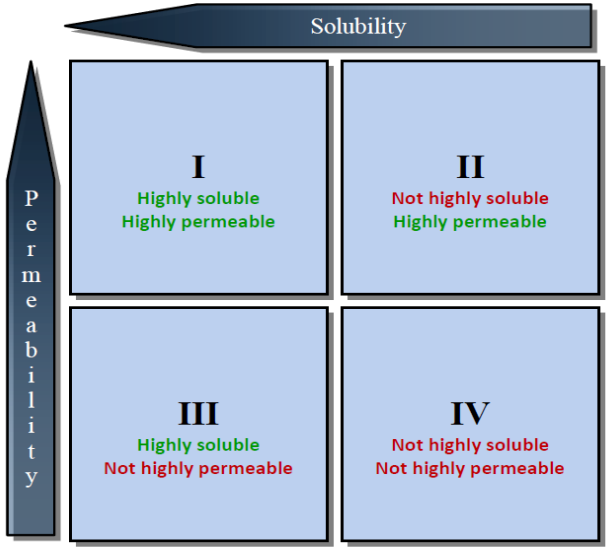
•Reducing time in bringing product to the market

•Reduce product cost

BCS-Classification

Biowaiver approval is based on the Biopharmaceutics Classification System (BCS)

(1995 Amidon et.al)



If the ***in vivo*** **dissolution** of a highly soluble compound is **rapid** and **excipients** used in the product **do not affect absorption of the API** then bioequivalence between the two pharmaceutically equivalent IR products **need not be demonstrated using *in vivo* studies**.

Timeline for evolution of biowaiver guidances

1995	SUPAC Guidances
2000	BCS based Biowaiver Guidance for Immediate Release Dosage Forms
2001	Note for Guidance on the Investigation of Bioavailability and Bioequivalence (Variations)
2003	Bioavailability and Bioequivalence Studies for Orally Administered Drug Products
2006	Biowaiver Guidance Annex 8 TRS 937
2010	Guideline on Investigation of Bioequivalence
2011	General notes on BCS based biowaiver applications (PQP Guidance document)
201?	Updates in progress to FDA biowaiver document..

Applicable dosage forms

BCS based biowaivers are

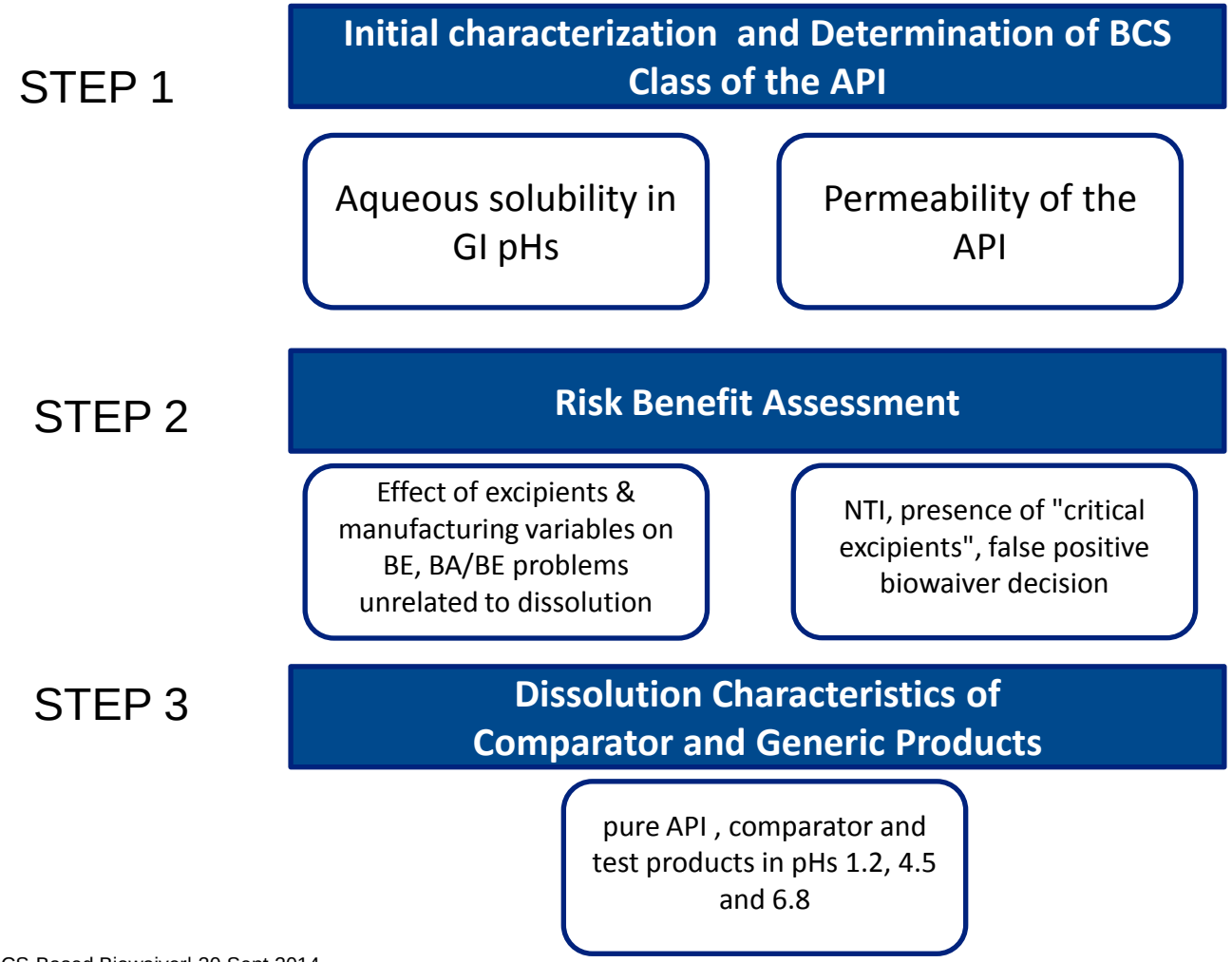
applicable to

immediate release, solid pharmaceutical products for **oral administration and systemic action** having the same pharmaceutical form

Not applicable to

sublingual, buccal and modified release formulations

Biowaiver procedure



BCS-based solubility

Highly soluble

Dose/Solubility ratio ≤ 250mL in aqueous buffers

pHs 1 – 6.8 (7.5) at 37 ± 1°C

Dose is defined differently in different guidances

- WHO- highest dose strength mentioned in the EML
- US FDA – maximum dose strength that is marketed
- EMA- highest single dose that is administered

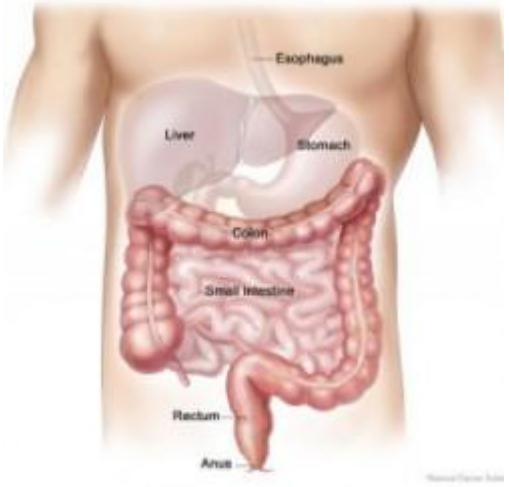
Medium	pH	D/S Ratio (mL) D=153mg base	D/S Ratio(mL) D=600mg base
Water	6.4	< 24.60	< 96.49
*SGF_{sp}	1.0	< 29.13	< 114.25
*SGF_{sp}	1.2	< 23.06	< 90.7
Acetate buffer	4.5	< 22.55	< 88.45
§SIF_{sp}	6.8	62.94	246.85
§SIF_{sp}	7.0	1478	-
§SIF_{sp}	7.5	9243	-

Dose solubility ratios for amodiaquine hydrochloride in aqueous buffer at 37 °C

Permeability

Highly permeable

APIs with a permeability of ≥ 85% (≥ 90%) of the administered dose are defined as highly permeable



Primary data (in humans)

- Absolute bioavailability
- Mass balance studies
- Intestinal perfusion studies

Secondary data

- Perfusion studies in animals
- *In vitro* permeability studies using CaCo-2 or MDCK cell lines along with reference substances

http://drjoelrosen.com/2011/05/intestinal-permeability/

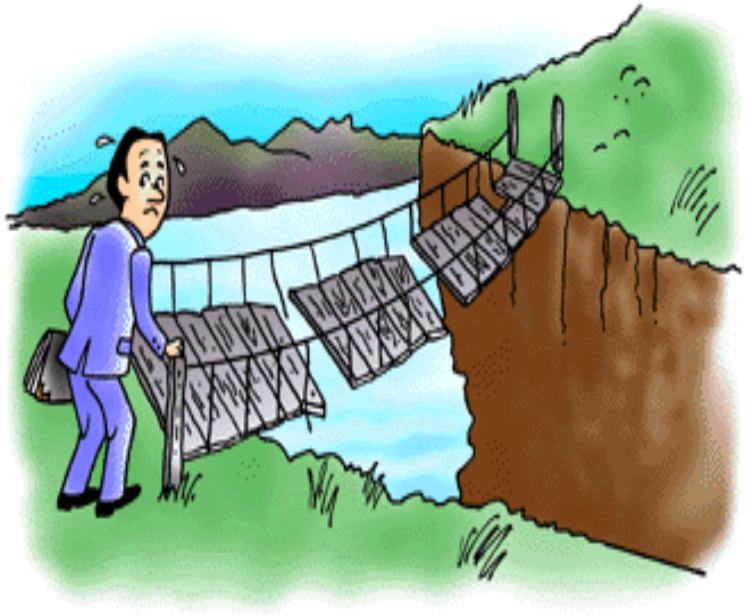
Comparison between Guidances: BCS Class

Class eligible for a biowaiver	Biowaiver guidances		
	FDA	EMA	WHO
I			
II			(weak acids only)
III			
IV			

Rickety turf

- Different derivatives of the API in test and comparator (salts that exhibit different solubility characteristics)
- Different polymorphs in test and comparator
- Poorly soluble drugs (most Class II and Class IV API)
- Reports of bioinequivalence not related to dissolution

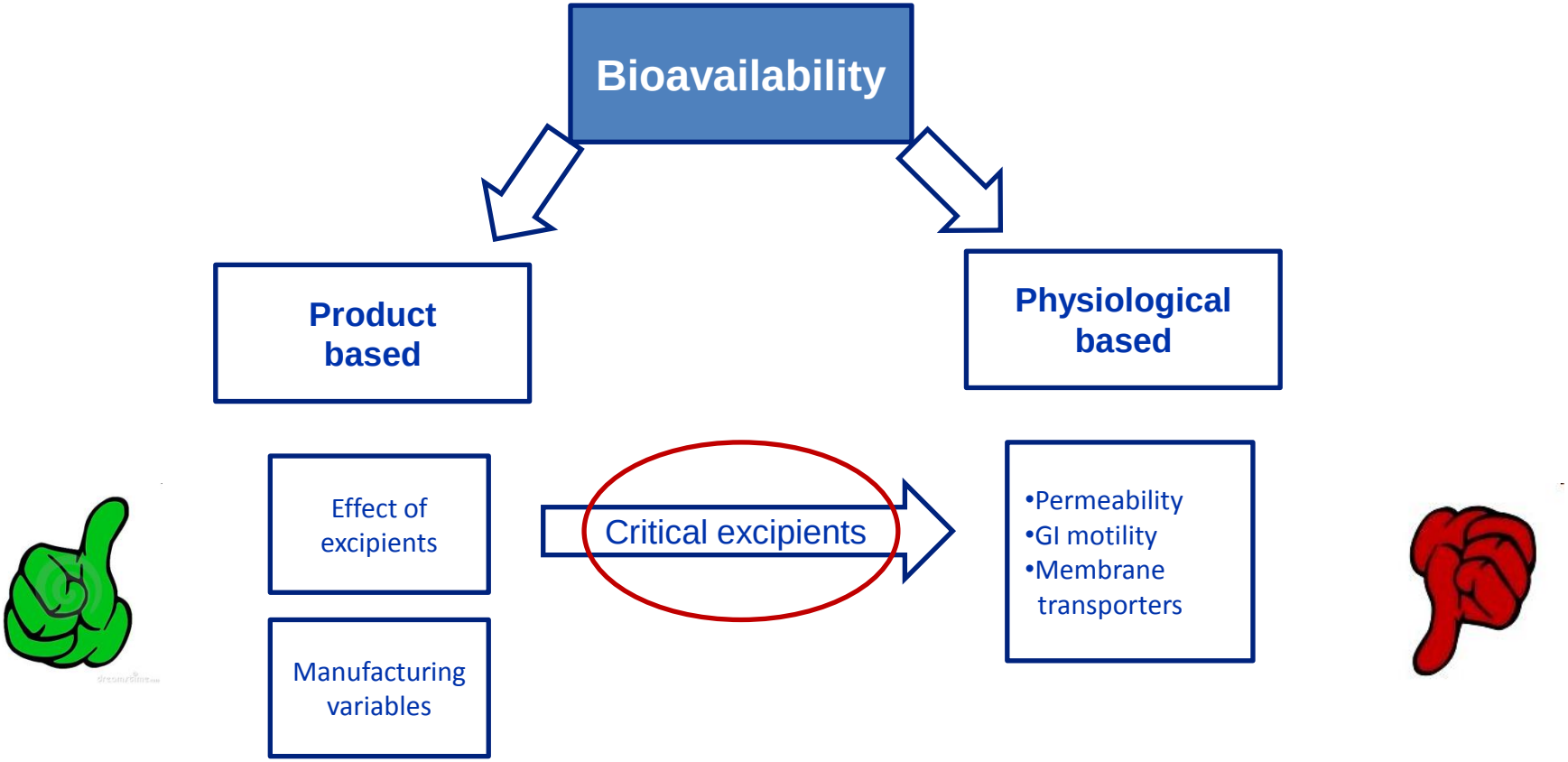
  E.g. quinine sulfate



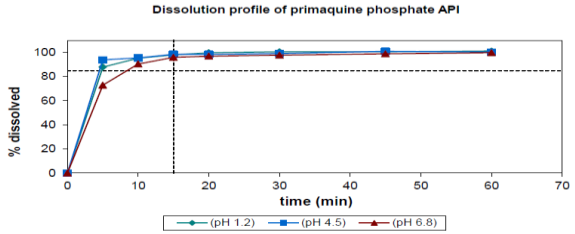
APIs with **Narrow therapeutic index (NTIs)** are a **"NO GO"** for biowaiver approach

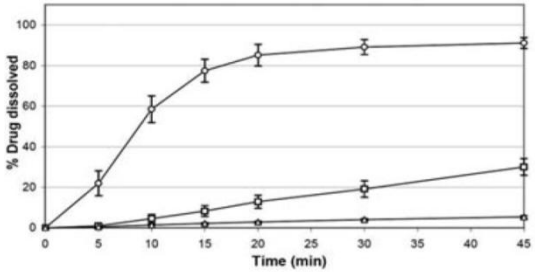
Risk assessment

For the purpose of biowaiver "risk" can be defined as a "false positive" decision and the ramifications of such a product on patient safety

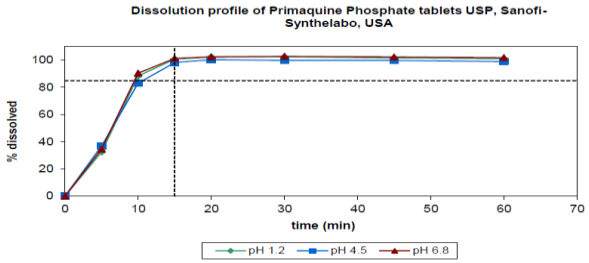


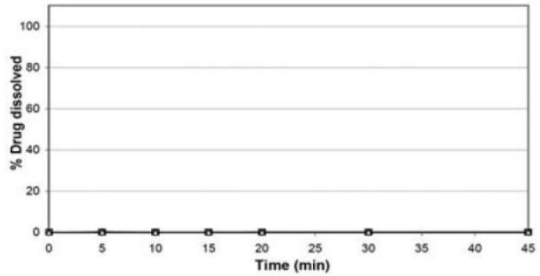
Effect of formulation and manufacturing variable



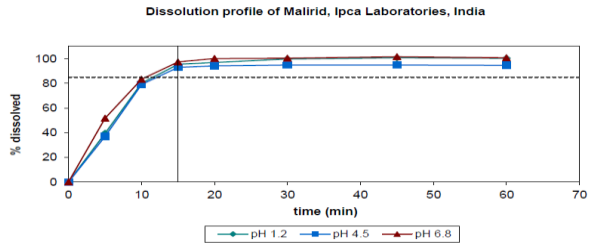


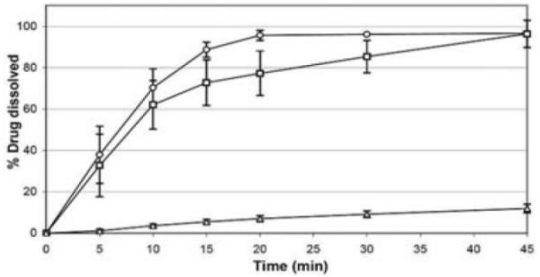
Qualaquin®





Obd Chininii sulfatis 250 mg





Pure drug

Nair et al. Biowaiver monographs for immediate release solid oral dosage forms: Primaquine, J. Pharm Sci., 101 (3), 2012

Strauch et al. Biowaiver monographs for immediate release solid oral dosage forms: Quinine sulfate, J. Pharm Sci., 101 (2), 2012

Effect of excipients

Excipients that might affect bioavailability through non-dissolution mechanisms should be identified

e.g. sorbitol, mannitol, SLS and other surfactants.

Their impact on

- GI motility,
- susceptibility to interactions with the drug substance,
- drug permeability and
- interactions with membrane transporters should be discussed.

These excipients should preferably be qualitatively and quantitatively the same as in the reference product.

Risk benefit analysis

The risk associated with a „false positive“ biowaiver decision should be considered.

Bioavailability related issues like

- Previous cases of bioinequivalence reported that are not related to the dissolution
- Effect of supra or sub therapeutic drug levels in patients

The risk of a false biowaiver decision should not outweigh the the benefits of a biowaiver procedure

Dissolution test conditions

Apparatus:	Paddle or Basket
N:	12
Volume of the medium:	900mL or less
Temperature of the medium:	37±1°C
Agitation speed:	75rpm (paddle) → WHO
	50rpm (paddle) → FDA/EMA or
	100rpm (basket)
Sampling times:	eg. 10, 15, 20, 30,45 60 min
Media:	SGFsp, pH 1.2
	Acetate buffer, pH 4.5
	SIFsp, pH 6.8
	(note: no surfactants)

Dissolution of pure API and products

- The test and the comparator products should be subjected to exactly the same battery of BCS-conform dissolution tests.

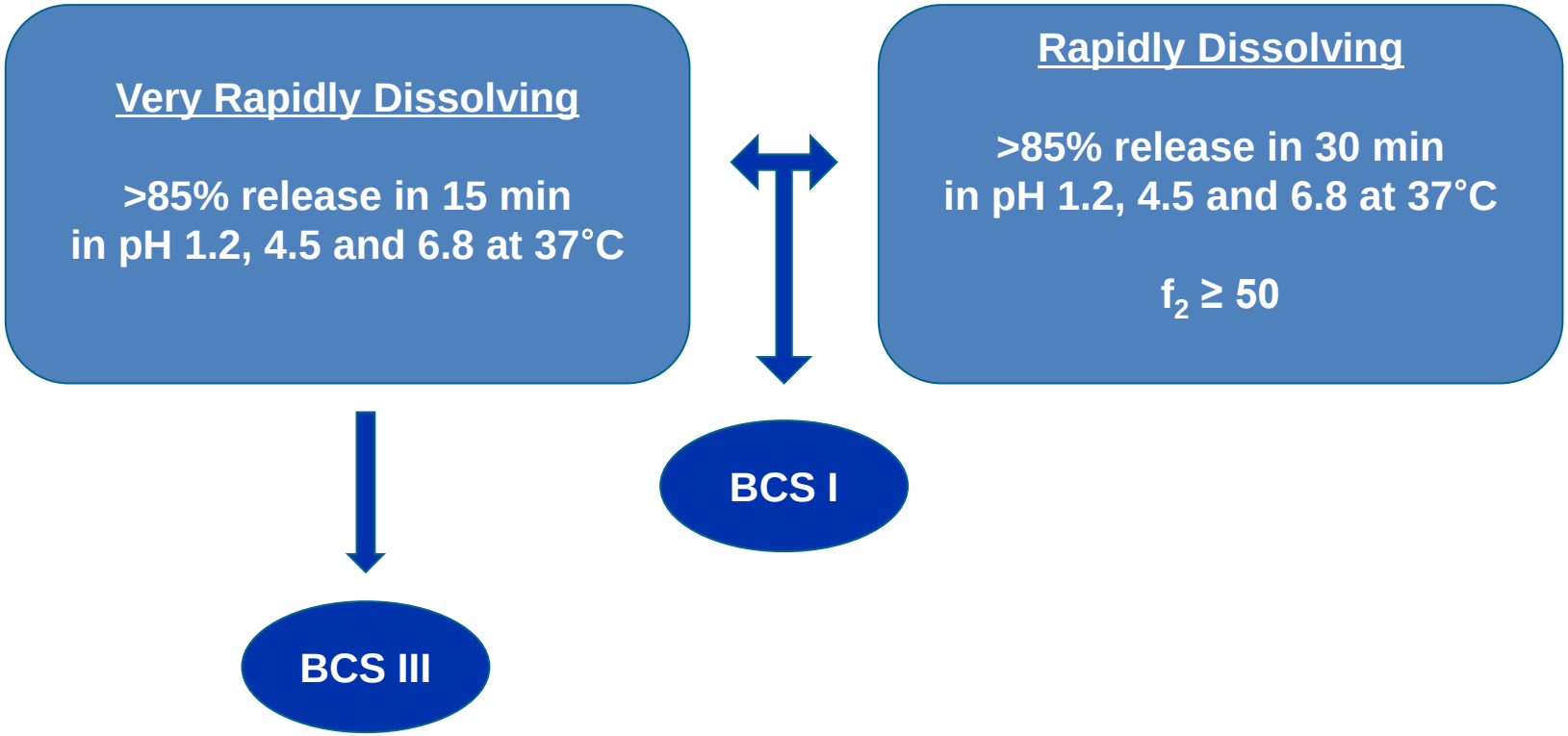
- Subjecting the **pure drug substance** to the series of dissolution studies as for the comparator product is a good approach to understand the drug behavior with respect to dissolution.

  e.g. wetting problems or if particle size needs to be reduced.

- The test conditions for Class I and III (II) APIs are the same but the evaluation criteria differs.

- It should be noted that the standard quality control dissolution test are usually not relevant for the biowaiver procedure.

Dissolution Criteria for Biowaiver



BCS Class II: Poorly Soluble and Highly Permeable (WHO only)

- "rapidly dissolving" product i.e. > 85% drug dissolution in 30 min from both comparator and test product in aqueous buffer at pH 6.8 at 37°C

ISSUE

If the comparator cannot meet the dissolution test criteria , biowaiver based approval is not possible

Possibilities!!!!

Either locate an acceptable alternative (as comparator listed in various jurisdictions could differ) or demonstrate BE by *in vivo* studies.

Summary

- Biowaiver procedure is a surrogate method of evaluating bioequivalence of generic products
- Just by belonging to Class I/III and/or fulfilling dissolution criteria does not entitle a product eligibility for a biowaiver approval
- Biowaiver decision can be arrived upon after evaluating the biopharmaceutical and clinical properties of the drug and the product.
- NTIs are NOT biowaiverable
- If critical excipients are used , then explanation regarding their choice and amounts need to be given to the regulatory authorities
- the risk associated with a „false positive“ biowaiver must not outweigh the benefit of applying a biowaiver procedure

Useful links

U.S. Department of Health and Human Services :Food and Drug Administration Center for Evaluation and Research (CDER). 2000 Guidances for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on Biopharmaceutics Classification System Accessed on January 10, 2011 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf

European Medical Agency. 2010 COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE: Guideline on the Investigation of Bioequivalence Accessed on December 5, 2012 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

World Health Organization (WHO) 2006 Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Accessed on January 10, 2011 at http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=403

Thank you for your attention

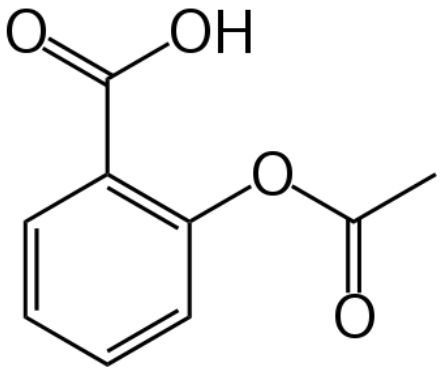
Back up

ACETYL SALICYLIC ACID

"Gastrointestinal Instability"

Acetylsalicylic acid

Category:	Non steroidal anti-inflammatory
Single Dose :	300-1000mg
pK_a:	3.5
Log P:	1.18
Therapeutic index:	wide
Permeability:	high
Risk assessment:	minimal



Challenges

•Acetylsalicylic acid (ASA) is prone to pH dependent hydrolysis to salicylic acid

•Salicylic acid (SA) is an active metobolite and hence the relevance of conversion of SA for a biowaiver decision needs to be evaluated

- ❖ *Stability indicating dissolution experiments*
- ❖ *Modified solubility experiments need to be performed*

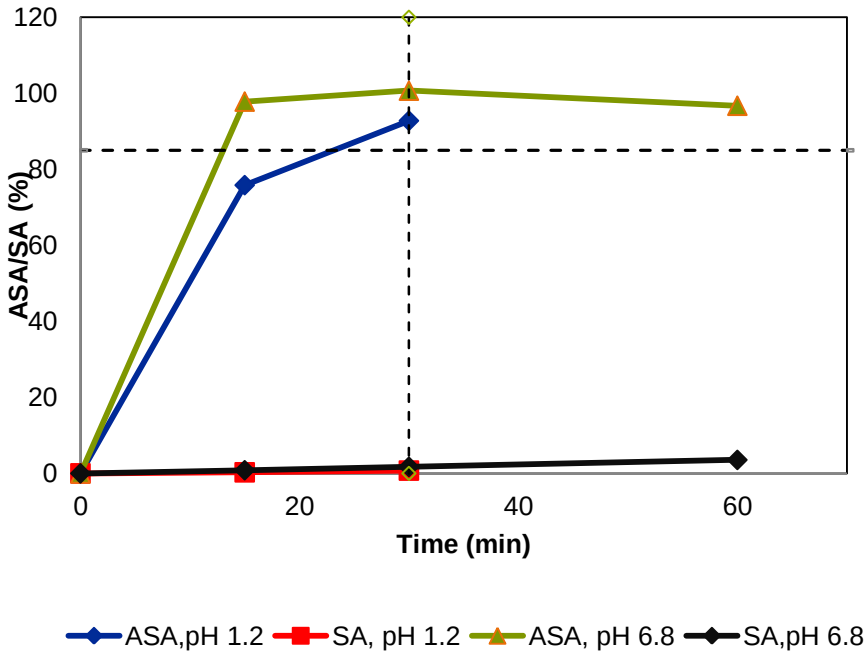
Solubility and Dissolution Results

The goal of the solubility experiments was to demonstrate

Medium	Shaking time (min)	Final pH	Average amount (mg) dissolved in 250ml	Dose/solubility ratio Max. Dose: 1000 mg
0.1N HCl, pH 1.0	45	1.1	1176	<212.76
Phosphate buffer, pH 3.5	20	3.0	1251	<199.84
Acetate buffer, pH 4.5	15	3.5	1655	<151.05
Phosphate buffer, pH 6.8	15	3.6	1910	<130.89

The dose solubility ratio of ASA calculated using solubility data estimated at 37ºC. Buffer concentrations were 50mM.

Dissolution studies on ASA tablets show that hydrolysis of ASA without enzymatic assistance is rather slow



SA contributions to solubility and dissolution from ASA formulations in the framework of the biowaiver can be considered negligible