HISTORY OF BIOWAIVER

1. The term "**biowaiver"** is **applied to a regulatory drug approval process** when the dossier (application) is approved based on evidence of equivalence **other than through In-vivo equivalence testing**.
2. **In 1995,** the American **Department of Health and Human Services, US Food and Drug Administration (HHS-FDA)** instigated the **Biopharmaceutics Classification System (BCS)**, with the aim of granting so-called biowaivers for SUPACs.
3. At that time the **biowaiver** was only considered for SUPAC to pharmaceutical products.
4. **More recently**, the **application of the biowaiver concept** has been extended to approval of certain orally administered generic products

INTRODUCTION

- A **Biowaiver** means that **in vivo bioavailability and/or bioequivalence studies** may be **waived (not considered necessary for product approval).** In short, In-vitro instead of In-vivo "Bioequivalence" testing.
- **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**.
- Only **APIs with high solubility and high permeability** and **which are formulated in solid, immediate release (IR) oral formulations can be approved on the basis of the Biowaiver procedure**.
- A **major advantage of the Biowaiver procedure is the simplification and reduction of time required for product approval**, thus **reducing the cost of bringing new products to market.**

CONT…

- The **risk of therapeutic inequivalence** 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 bioinequivalence 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**

BIOWAIVERS TYPE OF PRODUCTS

1. **SOLUTIONS**
2. **IV PRODUCTS**
3. **IMMEDIATE RELEASE PRODUCTS**
   - LOWER STRENGTH
   - BCS CLASS I
   - BCS CLASS II?
   - BCS CLASS III?
4. **EXTENDED RELEASE PROCDUCTS**
   - LOWER STRENGTH
5. **TOPICAL DOSAGE FORMS**
   - SOLUTIONS
   - AEROSOLS
   - ANTIFUNGALS
6. **INHALATION & NASAL DOSAGE FORMS (AERSOLS)**
   - SOLUTIONS

SCOPE & ADVANTAGES OF BIOWAIVER

SCOPE

❖ **Inside a product:**

- Scale up processes
- Line extensions
- Variation after marketing authorization

❖ **Between different products:**

- Application of generics without clinical data

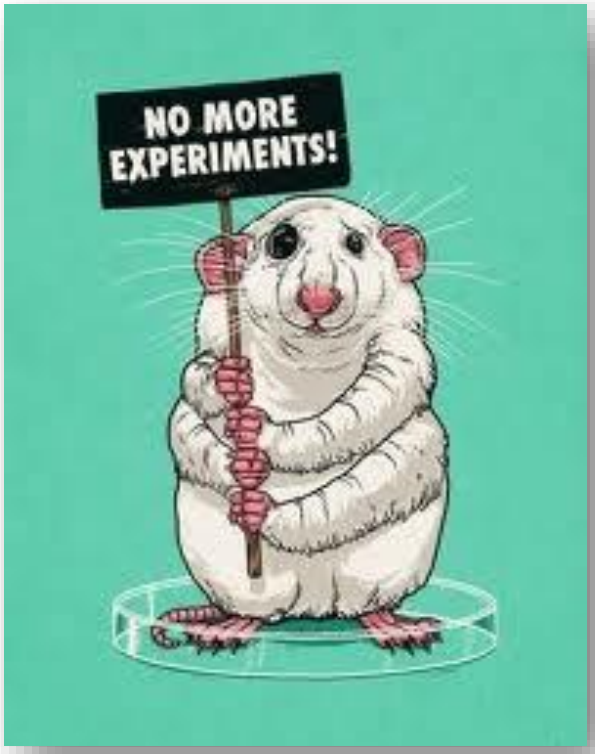


Fig. Source: INTERNET

ADVANTAGE'S

- Circumvent expensive and sometimes unethically questionable human testing.
- Reducing time in bringing product to the market.
- Reduce product cost

LIMITATION/EXCEPTION OF BCS-BASED BIOWAIVER

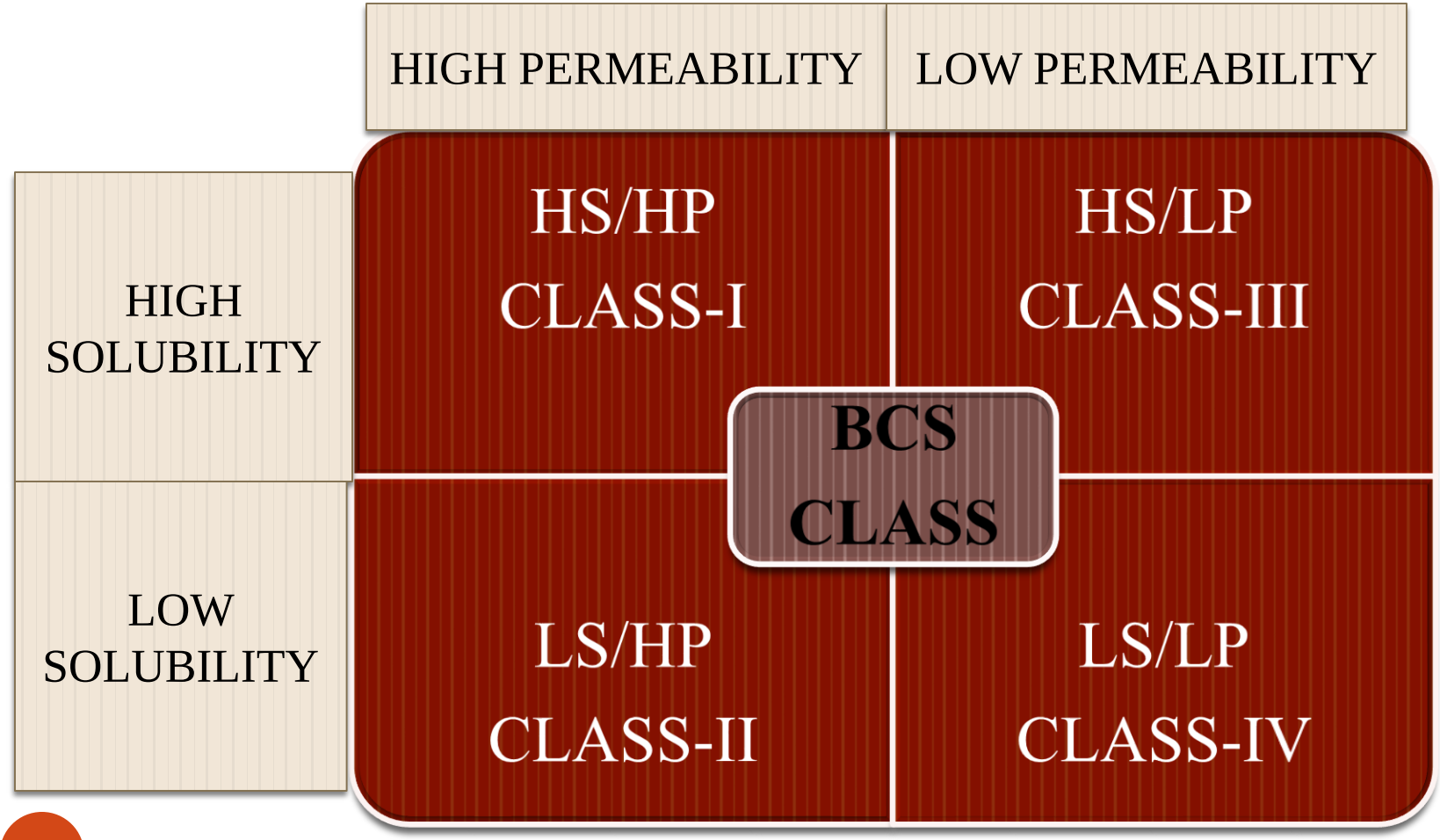
- **BCS based biowaiver are not applicable for the following:**

1. **Narrow therapeutic range drug products**. (It's definition is not mentioned in the guidelines acc. To EMA it must be **decided case by case**.)
2. BCS based biowaivers have **limited application for the class II drugs and not applicable for class III**.
3. Dosage form meant for absorption in the **oral cavity e.g. sublingual or buccal tablets**.
4. **Effects of food, absorptive transporters, efflux transporters, and routes of elimination (renal/biliary) were important determinants of overall drug absorption** and **bioavailability for immediate release oral dosage forms**, which are not considered in BCS.

BCS-BASED BIOWAIVER

- **According to the HHS-FDA definitions,**

the four possible categories for an API according to the BCS:



Source: INTERNET

BRIEF ABOUT BCS CLASS

BCS CLASS-1

- Compound are well absorption & high absorption rate as compared to excretion.
- Drugs exhibit High Abs. number & High dissolution number.
- **RLS** – Dissolution
- **If, dissolution is rapid** then gastric emptying rate will be RLS.
- **Examples**: Metoprolol, Diltiazem, Verapamil, Propranolol

BCS CLASS-2

- Bioavailability of these products is limited by their solvation rate.
- Drugs have a high absorption number but a low dissolution number.
- The absorption for class II drugs is usually slower than class I and occurs over a longer period of time.

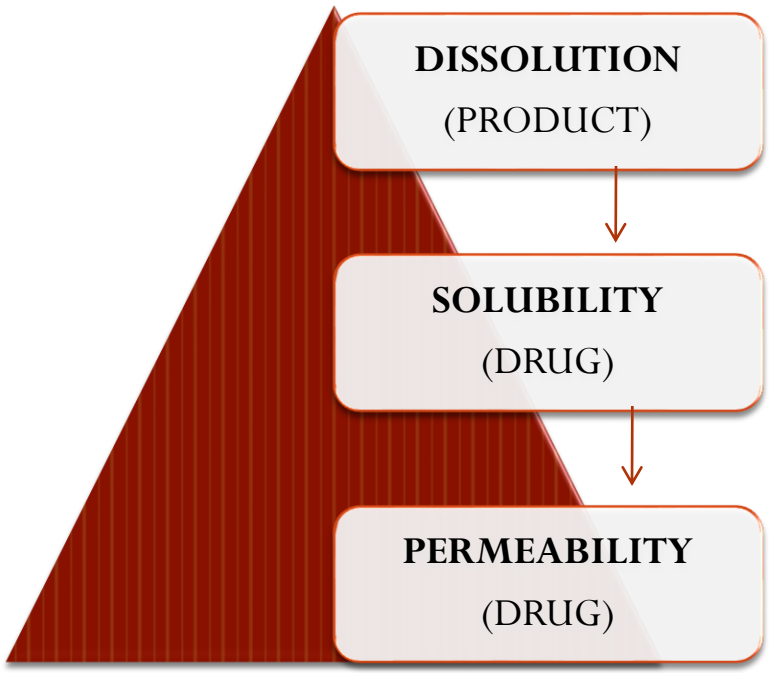
BCS CLASS-3

- The absorption is limited by the permeation rate but the **drug is solvated very fast**..
- If the formulation does not change the permeability or gastro-intestinal duration time then **class I criteria can be applied.**
- High variation in the rate and extent of drug absorption.
- Since the dissolution is rapid, the variation is an aspect to alteration of physiology and membrane permeability **rather than the dosage form factors.**
- **Examples**: Cimetidine, Acyclovir, Neomycin B and Captopril.

BCS CLASS-4

- These compounds have a poor bioavailability and not good absorbed over the intestinal mucosa properly
- Lot of problems for effective oral administration.
- **Examples :** Hydrochlorothiazide and Taxol.

BCS CLASS BOUNDARIES: OBJECTIVES



Very rapid/rapid dissolution - ensure that in vivo dissolution is not likely to be the "rate determining" step

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

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

This information is taken from the: WHO workshop on pre-qualification of medicines programme, Abu dhabi, 11-13 october, 2010 presented by Dr, JAN WELINK

DATA TO SUPPORT REQUEST FOR BIOWAIVERS

HIGH SOLUBILITY DEFINITION:

- The **highest single unit dose** is completely soluble in **250 ml** or less of **aqueous solution** at **pH 1 – 7.5 (37°C)**
- **250 ml**: derived from typical BE study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (approx. 250 ml) water

HIGH PERMEABILITY DEFINITION:

- According to **HHS-FDA,** when 90 % or more of the **orally administered dose** is **absorbed** in the small intestine.
- **Permeability** can be assessed by pharmacokinetic studies (for example, mass balance studies), or intestinal permeability methods, e.g. intestinal perfusion in humans, animal models, Caco2 cell lines or other suitable, validated cell lines.

CONT….

➢ Dissolution:

- In three different media: pH 1.2 HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer, composition in a paddle (50 rpm) or basket (100 rpm) apparatus at 37 °C and a volume of 900 ml.

A. Very Rapid Dissolution:

- An **IR drug product** is considered VERY RAPIDLY DISSOLVING when >85% of the labeled amount of drug substance dissolves within 15 minutes.

B. Rapid Dissolution:

- An **IR drug product** is considered RAPIDLY DISSOLVING when >85% of the labeled amount of drug substance dissolves within 30 minutes.

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:**

1. Dissolution Test in **3 different media (in 900 ml and at 37°C)** which are:
   - Buffer **pH 1.2**, Or simulated gastric fluid without enzymes or 0.1N HCl.
   - Buffer **pH 4.5**.
   - Buffer **pH 6.8** or simulated intestinal fluid without enzymes.
2. **12 samples in each media**, paddle rotating at 50 rpm or basket at 100 rpm.
3. **Sampling times are** 10, 15, 20, 30, 45 and 60 minutes**.**
4. The **profiles of the test and reference products must be similar in all three media.**

ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

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.

CONT..

- 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.**

To be considered bioequivalent according to the HHS-FDA biowaiver procedure

Or,

Eligibility criteria for biowaiver acc. to HHS-FDA

1. **BCS Class of API:-** **CLASS 1**
2. **Dissolution characteristics:** **Rapidly dissolving**, in three different media
   - **First Option:** Very rapidly dissolving and no further profile comparison
   - **Second Option:** Rapidly dissolving and Proving ***similarity of dissolution profiles of T and R*** *(e.g. using f2-test).*
3. **Excipients:-** **Must not influence the absorption of the API** (affecting motility or permeability).
4. **Therapeutic Index:-** **Not contain's an API with a narrow T.I**
5. **Formulation:-** **Product should not be designed to be absorbed from the oral cavity.**

To be considered bioequivalent according to the WHO biowaiver procedure

Or,

Eligibility criteria for biowaiver acc. to WHO

1. **BCS Class of API:-** **Class II acids with D:S ratio in 250ml or lower at pH 6.8 or >85% dissolved within 30 minutes at pH (75rpm) .**
   Class III compounds are eligible, if they dissolved within 15 minutes in buffer media ph 1.2-6.8 (75rpm).

2. **FILLING PROCEDURE:-**
   MUST NOT FOLLOW FDA, SHOULD BE STICK TO WHO GUIDELINES

3. **pH FOR SOLUBILTIY DETERMINATION:-** **1.2 TO 6.8**

4. **PERMEABILITY:-** **MUST BE HIGH (i.e., >85%)**

REGULATORY PROVISONS OF BIOWAIVERS : GLOBAL PERSPECTIVE; A COMPARATIVE APPROACH

PARAMETERS	US	EU	JAPAN
ALLOWED BCS CLASS	**I**	**I & III**	All
HIGHLY PERMEABLE	**>90%**	**>85%**	Not relevant
RAPIDLY DISSOLVING	**>85%** in **30 min**, at pH **3** (pH **1.0, 4.6 , 6.8**)	>85% in **15 min**, at pH **3** (pH **1.2, 4.5 , 6.8**)	No requirement
MEDIA SURFACTANT	**SUPAC allowed-** if justified.	None **"strictly discouraged".**	Required **if low solubility**
INTRA-MURAL COMPOSITION CHANGE	**SUPAC allowed- for all BCS classes.**	**Variation**	Type A-E, Type B, C, E like SUPAC level 1,2,3 Type D unique
IVIVC AS DOSAGE REGIMEN/BE SURROGATE	**Allowed for Moderate Release SUPAC**	**Allowed**	Not permitted

Source: INTERNET

CURRENT PEDESTALS OF BIOWAIVERS

BCS

- CONSIDER THE DOSE:SOLUBILITY RATIO, PERMEABILITY & DISSOLUTION BEHAVIOUR.

IVIVC

- BASED ON CORRELATION BETWEEN IN-VITRO DATA TO IN-VIVO PROFILE.

C.P

- NEW PRODUCT IS QUALITATIVELY SAME & QUANTITATIVELY PROPORTIONAL TO BIO-BATCH.

- **C.P :- COMPOSITION PROPORTIONALITY**
- **SOURCE ;- INTERNET**

APPLICATION OF BIOWAIVER

1 & 2

- FOR CHECKING VARIATIONS IN DRUG PRODUCTS
- FOR GENERIC DRUG APPLICATION

3

- DEVELOPING NEW DRUG PRODUCTS e.g., BRIDGING STUDIES, PILOT BATCH v/s PRODUCTION BATCH.

4

- BIOWAIVER MEANS TO OBTAIN WAIVE OFF FOR CARRYING OUT EXPENSIVE AND TIME-CONSUMING BA AND BE STUDIES.

CONCLUSION

- 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).**