BIOEQUIVALENCE AND THERAPEUTIC EQUIVALENCE

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Introduction

Early 1970's FDA regulations for submission of BA data

1984 US Congress passed the "Drug Price Competition and Patent Term Restoration Act of 1984" - authorizing FDA to approve generic Rx through BA and BE studies

- FDA published for the industry a series of drug specific BA/BE guidances, general guidances on conducting studies, and regulatory recommendations and statistical guidances to document BE

$\Rightarrow$ Approval of a large number of generic drug products

Introduction

- BA and BE have become the cornerstones for the approval of brand-name and generic drugs and have been utilized for brand-name drugs to reduce cost of development.

- Tremendous advances have been made in the area of assessment of bioequivalence. Currently approaches to determine BE of pharmaceutical products has been largely standardized.

- Continuing efforts by regulatory authorities and the scientific community, to understand and develop more efficient and scientifically valid approaches to the assessment of BE of various dosage forms.

Generic medicines: Overview

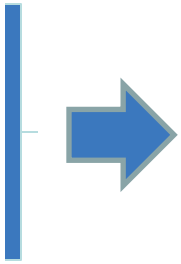
- Provide an affordable, gold standard medication for many major illnesses
- Allow access to medicines for a greater proportion of the population
- Deliver savings to national health bills
- Enable future long-term savings in the expanding role of medicines vs hospitalization
- Stimulate healthy competition with the branded sector
- Provide newer formulations and methods of delivery, etc, which provide incremental innovative improvements for patients
- Are high quality products

Generic Medicines: Essential contributors to the long-term health of society, IMS Health, 2010.

Why Bioequivalence Studies?

Brand Name Drug Requirements

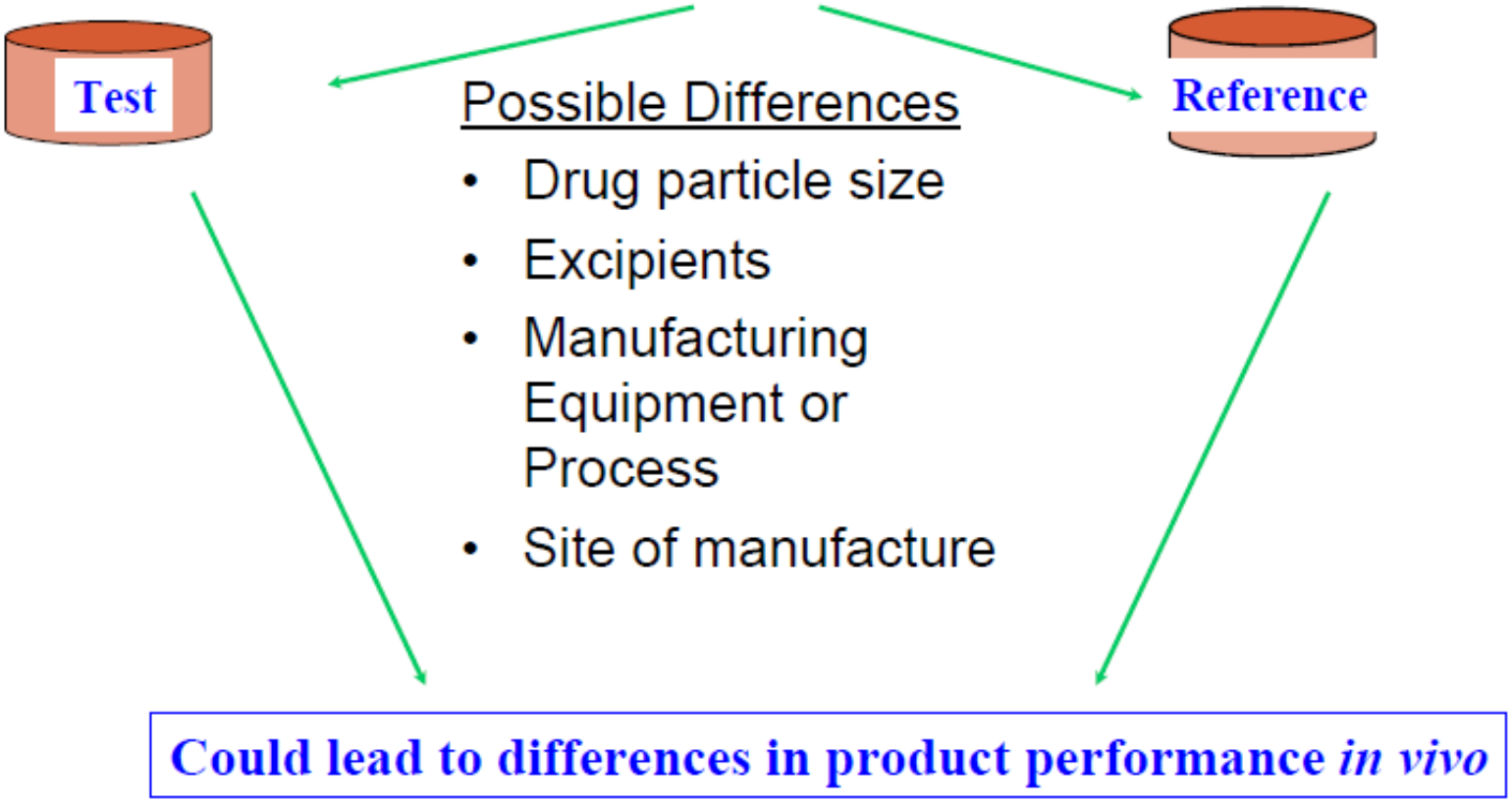
- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Animal studies
- Clinical studies
- Bioavailability



Generic Drug Requirements

- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Bioequivalence

Why Bioequivalence Studies?



Therapeutic Equivalence

To be safe and effective, generic drugs have to meet **the same rigid standards as the innovator drug.**

Two products are considered to be "therapeutic equivalents" if they each meet the following criteria:

1- They are **pharmaceutical equivalents**

Contain **the same active ingredient(s) as the reference listed drug (inactive ingredients may vary)**

Be **identical in strength, dosage form, and route of administration as the Reference Listed Drug**

2- Meet the same batch requirements for **identity, strength, purity and quality**

Therapeutic Equivalence

3- They are **bioequivalent (PK,** PD, Clinical**, In vitro)**

4- Have **the same use indications (labeling)**

5- They have been manufactured in compliance with **GMP**.

Therapeutic Equivalence

PHARMACEUTICAL EQUIVALENCE	+	BIOEQUIVALENCE	=	THERAPEUTIC EQUIVALENCE
*Same AI(s) *Same strength *Same dosage form *Same route of administration		*In vivo measurement of active moiety(ies) in biologic fluid		*Switchable under labeled conditions of use
Compared to the RLD		* In vivo pharmacodynamic comparison		
		* In vivo clinical comparison		
		* In vitro comparison		

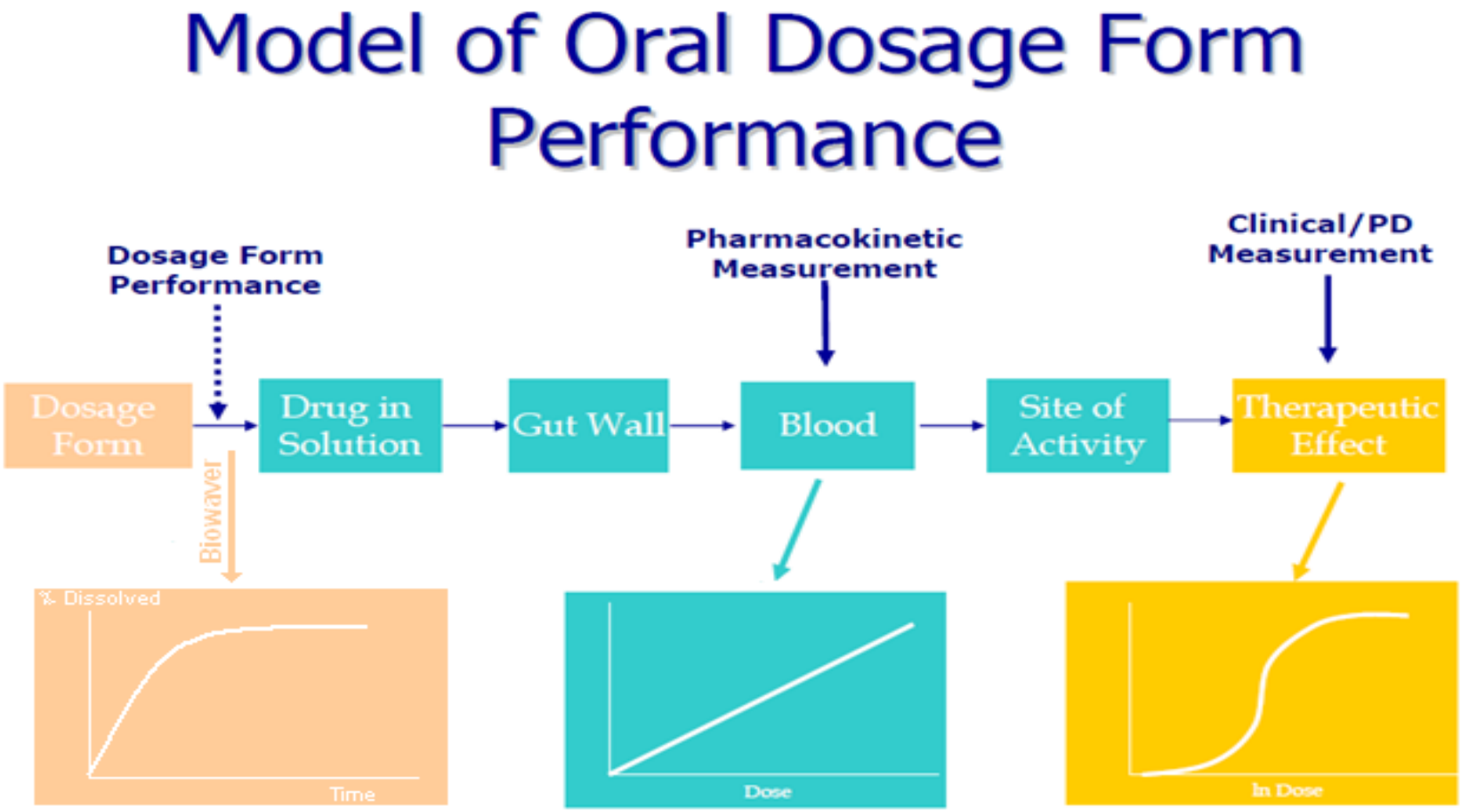
Therapeutic Equivalence

Pharmaceutical Equivalence + Bioequivalence
= Therapeutic equivalence

- Therapeutically equivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring.

- The most efficient method of determining TE is to assure that the formulations perform in an equivalent manner.

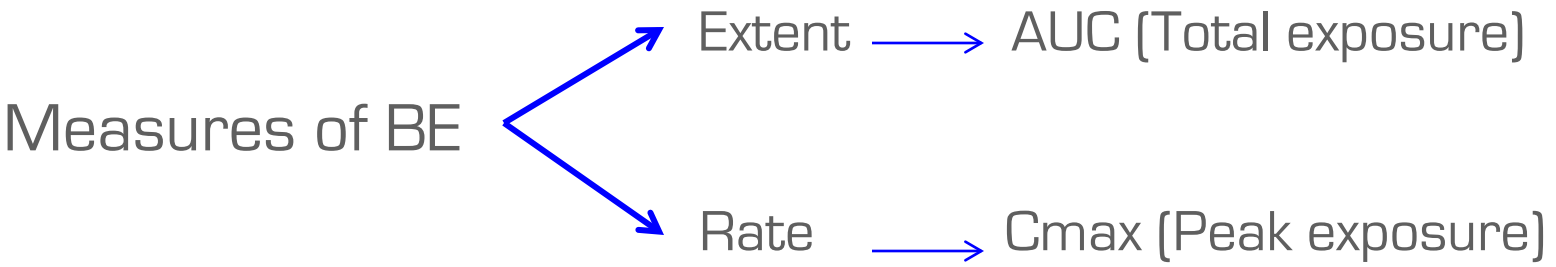
Bioequivalence



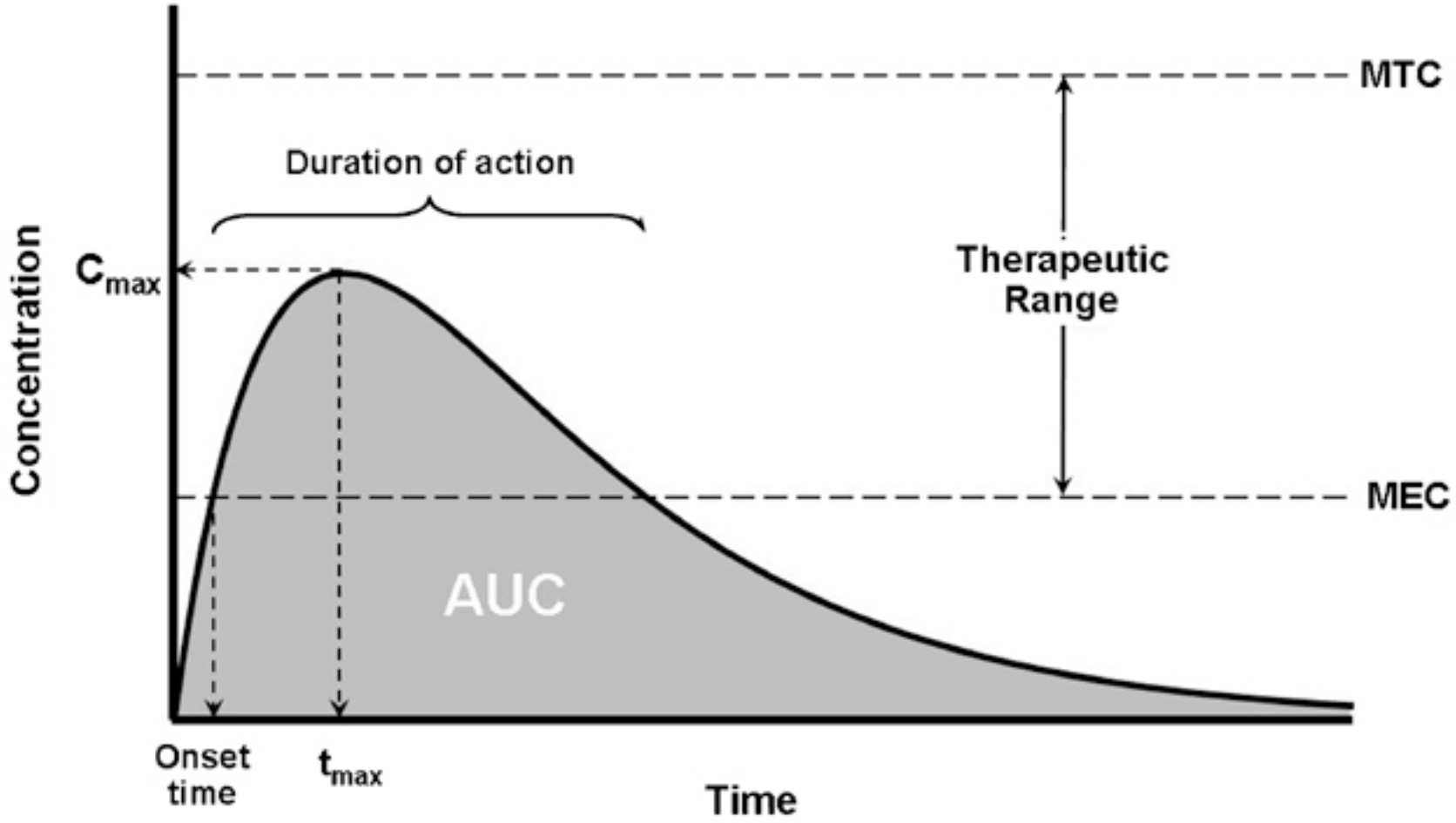
In vitro methods

Bioequivalence - Definition

The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives (T: Test; R: Reference) becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.



Bioequivalence - Definition



Concentration versus time curve

Bioequivalence - Definition

No statistically significant difference in the:

- Rate (C_{max} , Rmax)*
- Extent (AUC, $Ae_{(0\text{-}t)}$)* *

to which the active ingredient becomes available at the site of drug action

* *Cmax = maximum plasma concentration*

Rmax = maximum rate of drug urinary excretion

* * *AUC = area under the plasma-concentration vs time curve*

$Ae_{(0\text{-}t)}$ = cumulative amount excreted in the urine

Bioequivalence Study
(biological matrix)

- Conduct a study in healthy subjects, each receives Test (T) and Reference (R)
  - Standard design: randomized, two-period, two-sequence single dose crossover design
  - assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product
  - administered with about 8 ounces (240 milliliters) of water under fasting conditions, (highest/ lowest marketed strength).
  - Adequate washout period (e.g., more than 5 half lives of the moieties to be measured)

Bioequivalence Study

- Samples should be collected:
  - for 3 or more terminal half lives
  - for 72 hours for long half lives drugs, to ensure completion of drug product's GI transit time and drug absorption
- Obtain PK Parameters (AUC and Cmax) for each subject for the T and R products

Bioequivalence Study

Two one-sided statistical tests are carried out using log-transformed data from the bioequivalence study to show that the 90% confidence interval for the ratio of AUC and Cmax of the generic to the RLD is within the limits of 0.8 to 1.25

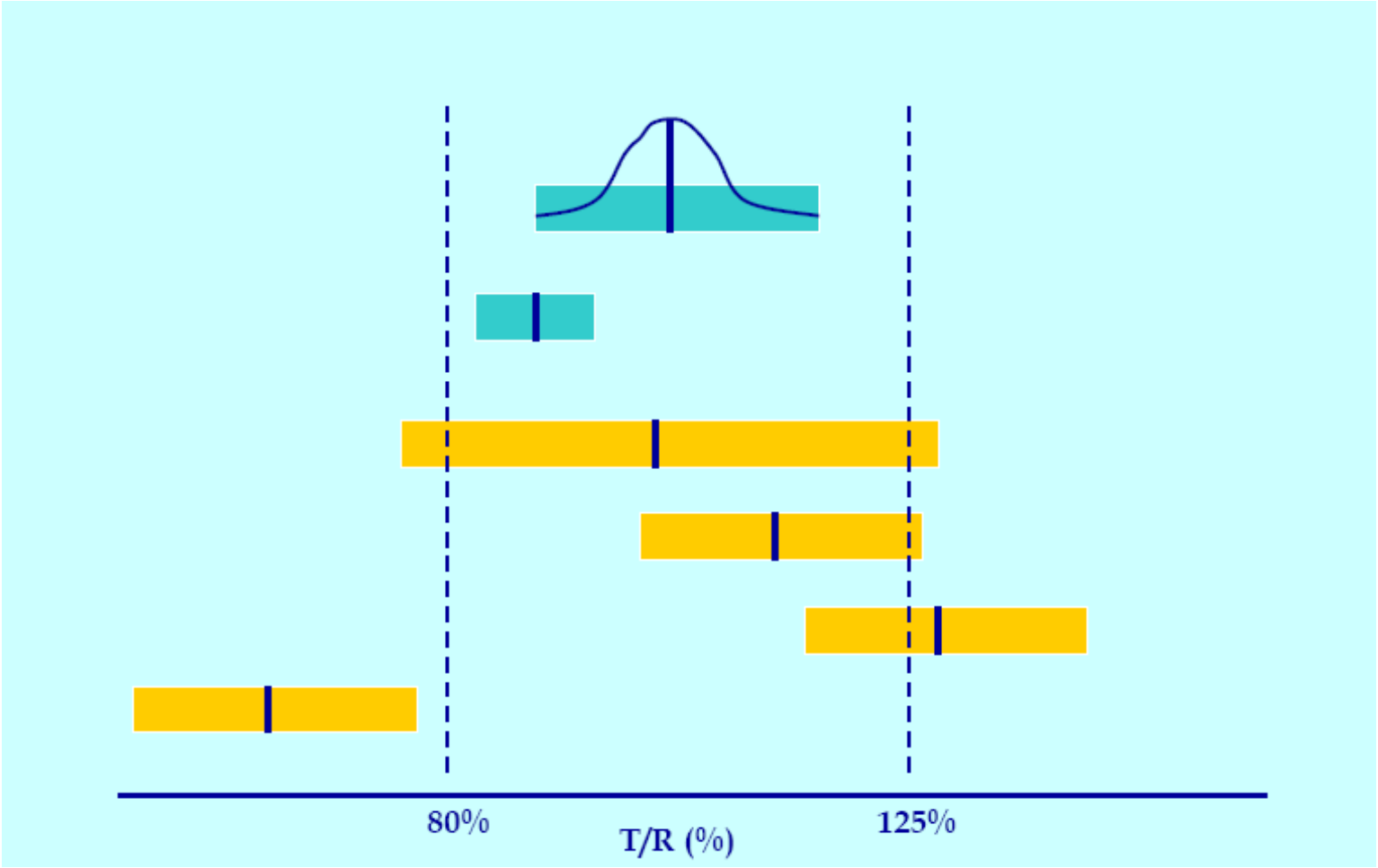
Current BE Requirements

- AUC: 90% Confidence Interval Limits 80-125%
- C_{max}: 90% Confidence Interval Limits 80-125%
- NTI: AUC and/or C_{max}: 90-111.11%**
- HVDP: (intra-subject variability>30%): wider acceptance range for Cmax**

Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations. Food and Drug Administration, Rockville, MD, 2003.

** *EMA Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *, January 2010.*

Possible BE Results



Bioequivalence Studies

FDA evaluated 2,070 human studies conducted between 1996 and 2007.

- The average difference in absorption into the body between the generic and the brand name was 3.5 percent.
- In studies in which brand name drugs were compared with themselves as well as with a generic: the difference for the **generic-to-brand comparison** was about the same as the **brand-to-brand comparison**.
- There will always be a slight, but not medically important, level of natural variability – just as there is for **one batch of brand name drug compared to the next batch** of brand name product.

Davit et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother. 2009.

Bioequivalence Studies

Generic Applications in 1997

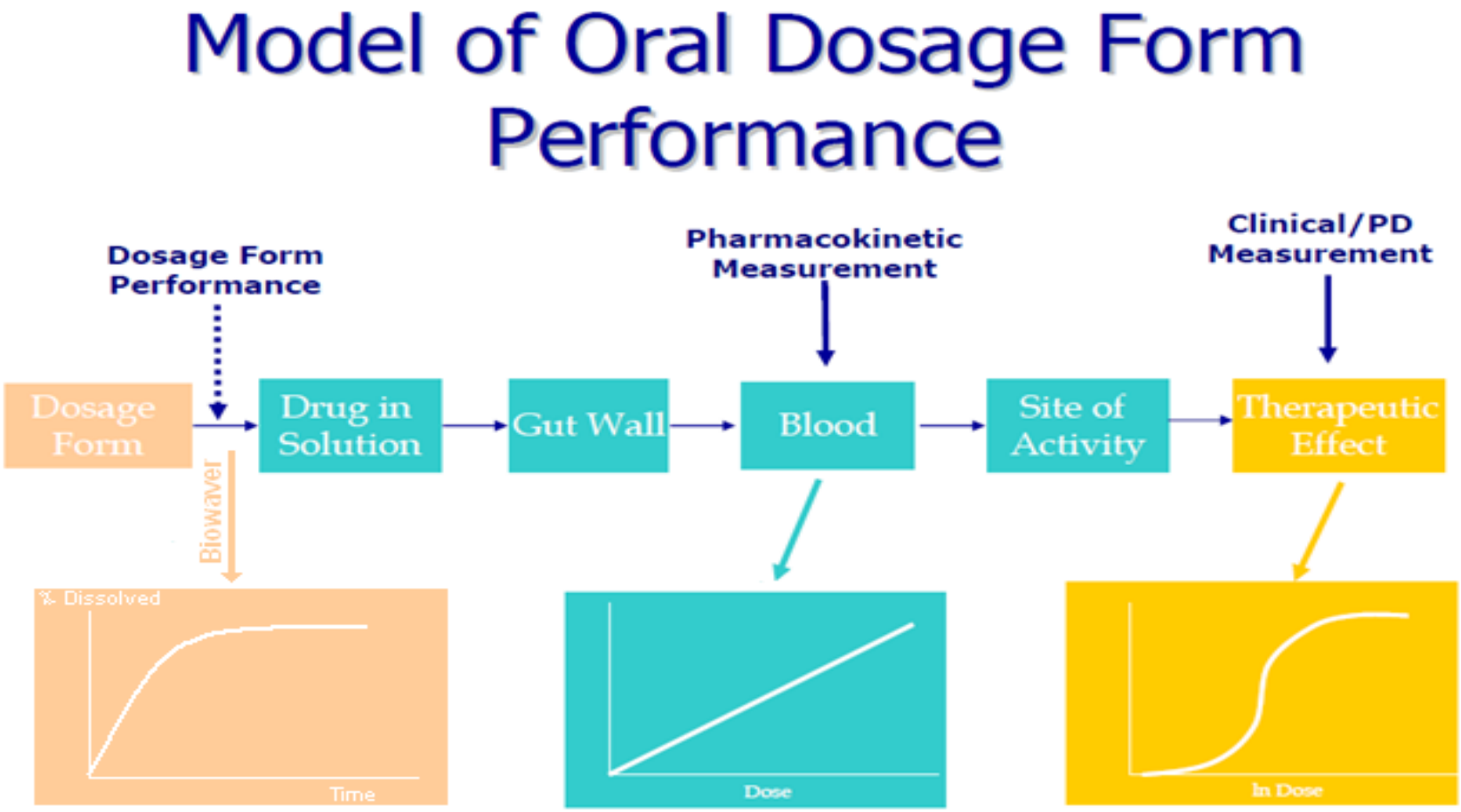
For 127 in vivo bioequivalence studies

- $AUC_{0\text{-tlast}}$ 3.47 ± 2.84%
- $AUC_{0\text{-infinity}}$ 3.25 ± 2.97%
- Cmax 4.29 ± 3.72%

Note that the mean difference between generic and innovator products is less than the 5% minimum mean difference in content uniformity allowed by the USP for the innovator (and generic) product.

J.E. Henney, JAMA 282: 1995, 1999.

Bioequivalence Studies



In vitro methods

Biowaivers

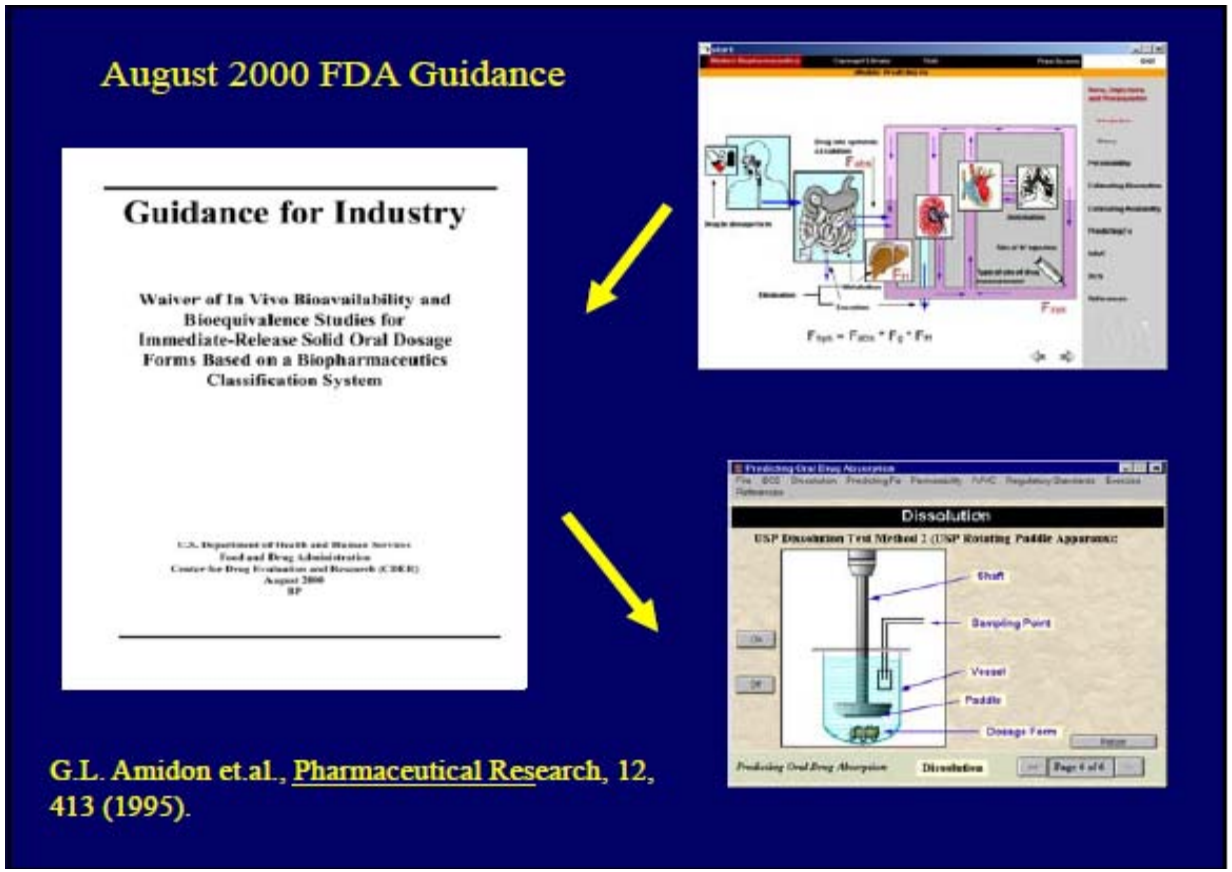
Waiver of *In Vivo* BE Studies...

Not waiver of BE!

Based on the Biopharmaceutics Classification System (BCS)

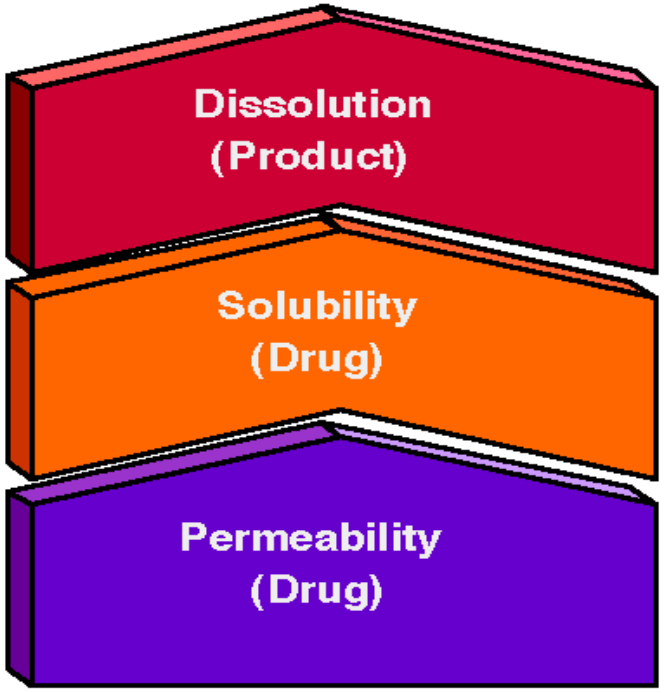
Biowaivers

Predict in vivo pharmacokinetic performance of Rx
Correlate in vitro drug product dissolution and in vivo BA
Extension of the BCS concept for approval of oral generic Rx



Biowaivers - Scientific Rationale

Covers the three main factors which govern the rate and extent of drug absorption from IR solid oral dosage forms :



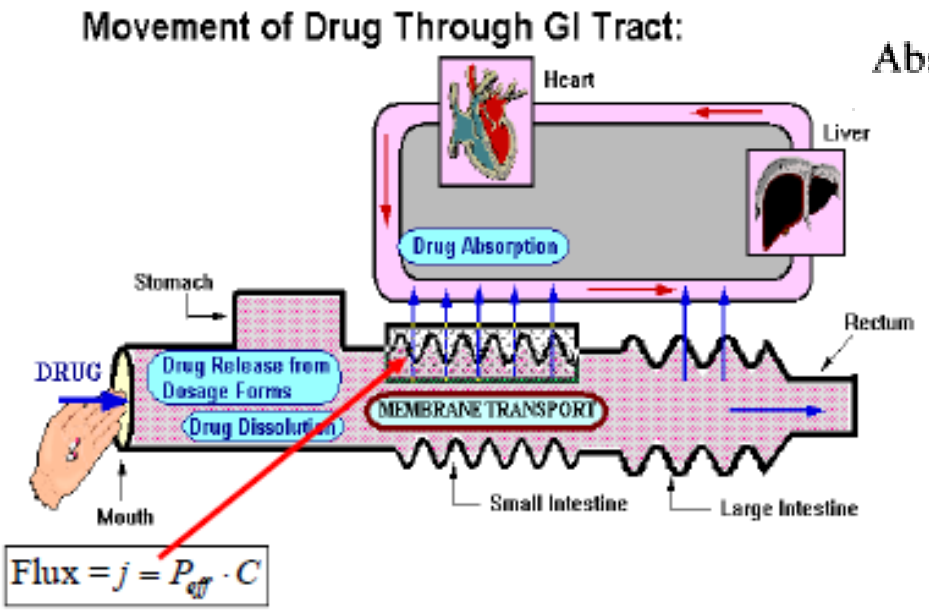
Rapid dissolution - ensure that in vivo dissolution is not likely to be the "rate determining" step

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

Biowaivers - Scientific Rationale

- BCS takes a mechanistic approach to setting BE standards: mass transport in the GI tract



$$\text{Absorption Rate} = dm / dt = \int\int_A P_w C_w dA$$

$$M(t) = \int_0^t \int\int_A P_w C_w dA dt$$

Amidon, 1995

Biowaivers - Scientific Rationale

- Drug is absorbed through the intestinal membrane at a rate that is proportional to the concentration at the membrane surface.
- The dissolution of the drug product in vivo determines the membrane surface concentration of drug.

The science of BE is at the absorption site

THUS:

- Similar In vivo dissolution→ similar in vivo absorption → Similar Systemic availability (BE)
- In Vitro dissolution methodology must capture the most important rate controlling in vivo dissolution process

BCS - Definition

- Scientific framework which divides APIs into four groups, according to their solubility and their permeability properties. (Amidon et al., 1995)

	High Solubility	Low Solubility
High Permeability	**Class 1** High solubility High permeability	**Class 2** Low solubility High permeability
Low Permeability	**Class 3** High solubility Low permeability	**Class 4** Low solubility Low permeability

Eligibility criteria for biowaiver

- ✓ BCS classification of the API: solubility and permeability
- ✓ Dissolution characteristics
- ✓ Stability in the GI tract
- ✓ Nature of the excipients - may influence motility and/or permeability in the gastrointestinal tract.
- ✓ Therapeutic Index
- ✓ Formulation: product not designed to be absorbed from the oral cavity and not MR
- ✓ Risk assessment

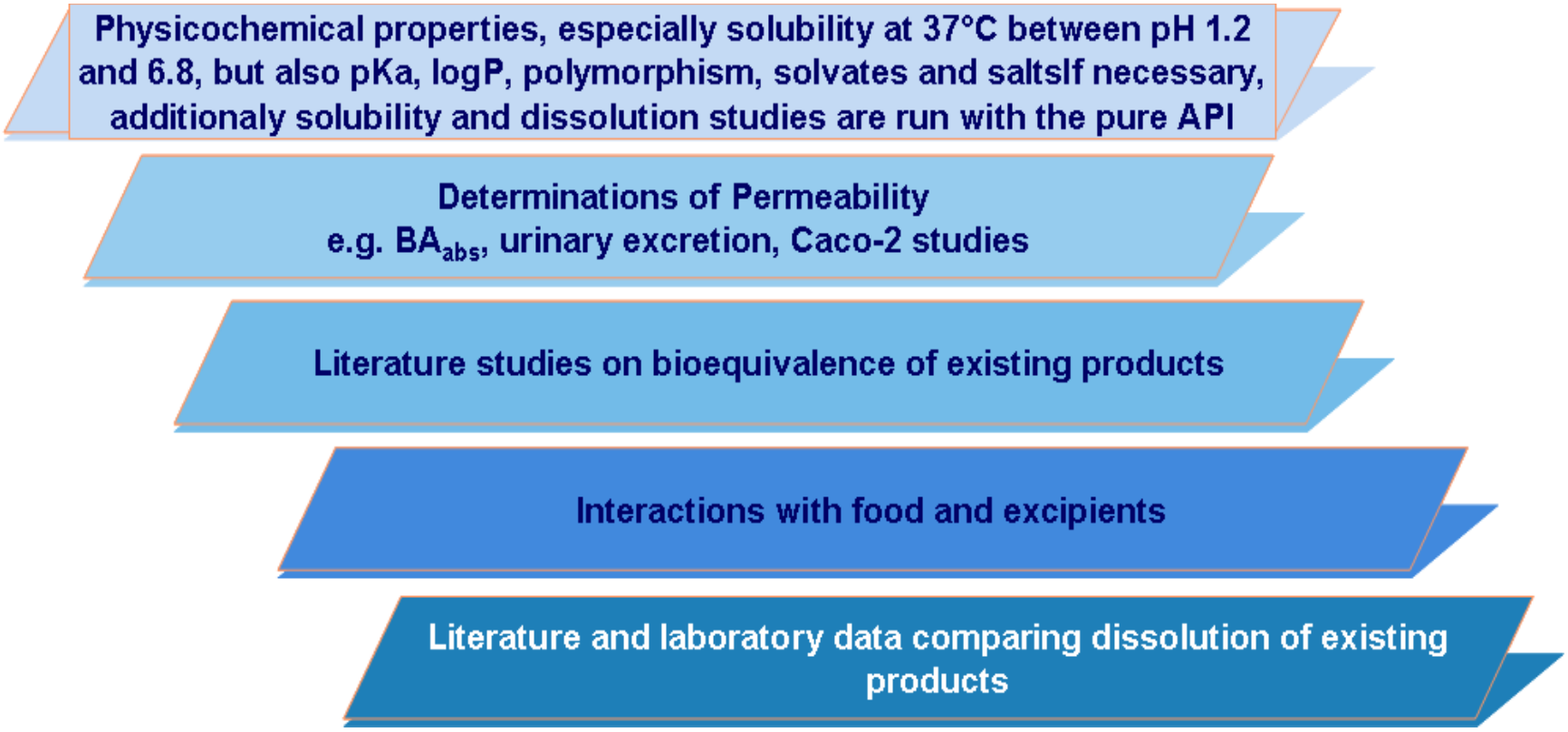
Biowaiver Monographs

- An initiative of the Federation Internationale Pharmaceutique (FIP).
- The aim is to evaluate all relevant data from the literature, for a given API, to assess the risk associated with a biowaiver
  - RISK = probability of an incorrect biowaiver decision
  - RISK = consequences of an incorrect biowaiver decision in terms of public heath and individual patient risks.
  - RECOMMENDATION = Biowaiver
- No formal regulatory status but represents the best current scientific opinions
- The approach includes all factors considered in the WHO Document:

„Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms." Technical Report Series, No 937, 40th Report, Annex 8 of WHO Expert committee on specifications for pharmaceutical preparations

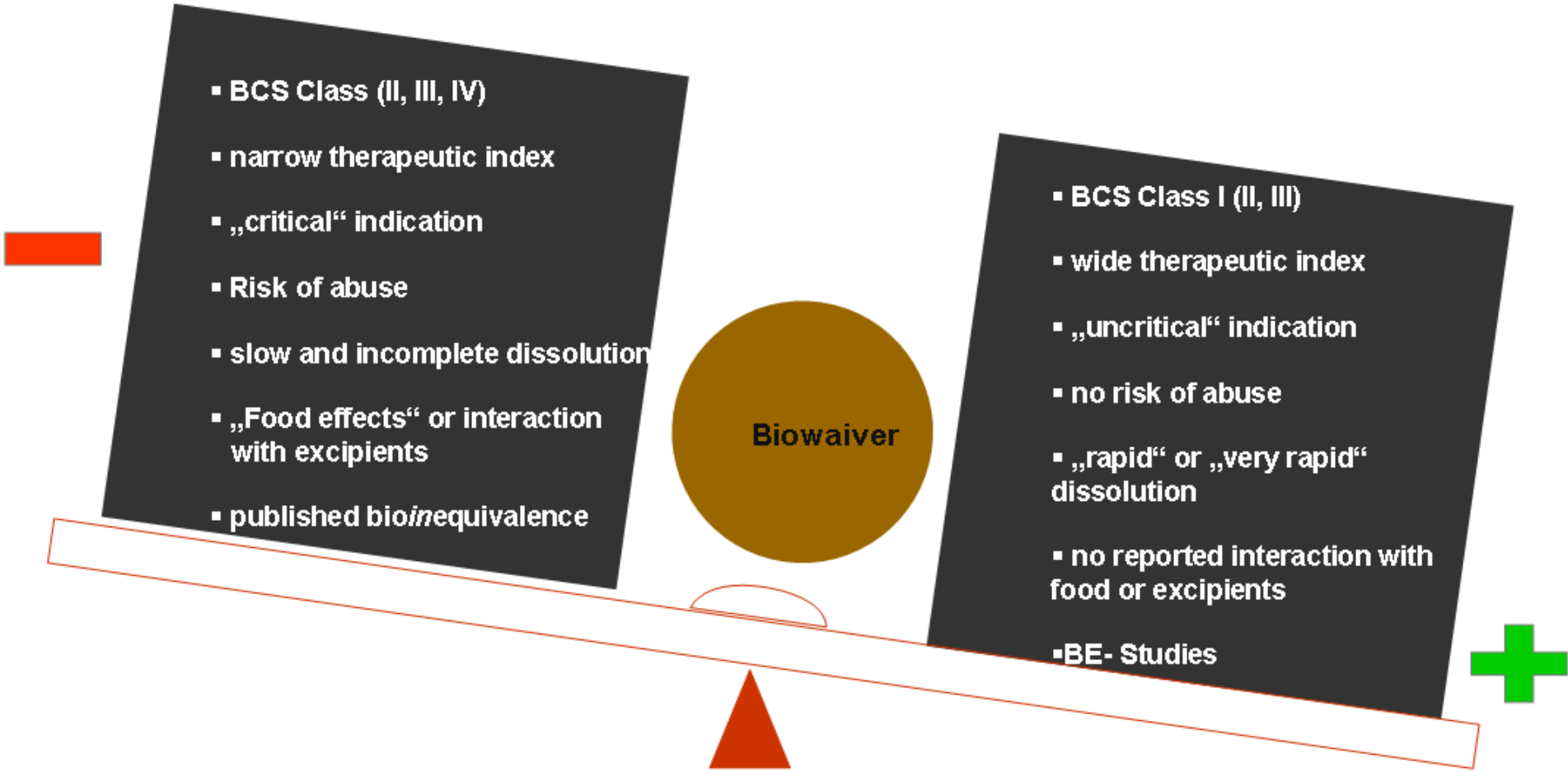
Biowaiver Monographs

What is taken into consideration?



Biowaiver Monographs

Evaluation of the collected Information



Prof. Dr. Jennifer Dressman & Corina Becker, 2007

Published Biowaiver Monographs

- Acetaminophen = Paracetamol
- Acetylsalicylic acid
- Amitriptyline Hydrochloride
- Atenolol
- Chloroquine Phosphate
- Chloroquine Hydrochloride
- Ciprofloxacin Hydrochloride
- Codeine Phosphate
- Diclofenac Sodium
- Efavirenz
- Furosemide
- Isoniazid
- Lamivudine
- Mefloquine Hydrochloride
- Metronidazole
- Prednisolone
- Primaquine Diphosphate
- Pyrazinamide
- Quinine Sulfate
- Rifampicin
- Verapamil Hydrochloride

Acetazolamide
Aciclovir
Amodiaquine hydrochloride
Bisoprolol fumarate
Chloroquine Sulfate
Cimetidine
Fluconazole
Diclofenac Potassium
Doxycycline Hyclate
Ethambutol Dihydrochloride
Ibuprofen
Ketoprofen
Levofloxacin
Metoclopramide Hydrochloride
Piroxicam
Prednisone
Propranolol Hydrochloride
Quinidine Sulfate
Ranitidine Hydrochloride
Stavudine
Zidovudine
Ribavirin
Nifedipine
Levetiracetam

www.fip.org/bcs_monographs

A Decade of Biowaivers - FACTS

- FDA: Class 1 (HS/HP)
- EMA: Class 1, Class 3 (HS/LP)

- No incidents of Type I errors in the use of in vitro testing to assess BE of Class 1 drugs in the USA and EU. (Mehta 2002, 2007).

- Clinical performance of the majority of approved IR oral drug products essential for human health can be assured with an in vitro dissolution test (Dahan et al, 2009).

Therapeutic Equivalence

Does BE equate to comparable clinical efficacy and tolerability?

Therapeutic Equivalence

“ I don’t want my patient, my loved one, or me as the patient to have to take a generic drug product based only on blood level measurements, usually in healthy volunteers, that has not been tested in patients.”

- 60% of the new drug products that came onto the market in the US had never been tested in patients.
- No drug products that has been shown to be bioequivalent in healthy volunteers has then been demonstrated not to be bioequivalent in patient populations, even a specific subset.

Leslie Benet, PhD - UCSF

Therapeutic Equivalence

- **Misconceptions on: "bioequivalence", "efficacy", "safety", and "manufacturing standards" of generic medicines**

- MAINLY HPs over the age of 55 years…

- **CONCLUSIONS: educational campaigns** on bioequivalence, quality and safety.

Physician perceptions about generic drugs.
Harvard Medical School. Ann Pharmacother. 2011.

Therapeutic Equivalence
Positive list

BIOEQUIVALENT

=

THERAPEUTIC EQUIVALENT

THE ORANGE BOOK

(Approved Drug Products with Therapeutic Equivalence Evaluations, FDA)

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Positive list: substitution be limited to drugs on a specific list

AIM: To provide public information and advice to health professionals and agencies about drug product selection and to foster cost containment

Therapeutic Equivalence Positive list

- All FDA approved drug products listed
- Therapeutic equivalence codes
  - "A" = Therapeutically equivalent to other pharmaceutical equivalent products - Substitutable
  - "B" = Inequivalent, NOT Substitutable
- Expiration dates: patent and exclusivity
- Reference Listed Drugs = listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its registration file

Therapeutic Equivalence
Positive list

- Reference listed drug (RLD)
  - Most logical comparator product for which quality, efficacy and safety must be demonstrated
    - Innovator product
    - Market leader
    - Product available in another market
- In some categories: more than one RLD
  - Example: when different release mechanisms produce different clinical effects

    ER nifedipine: Adalat CC (Bayer) and Procardia XL (Pfizer) are each RLDs, but are not equivalent.

Therapeutic Equivalence Substitution

- Prescribability refers to the situation where a patient is initially being prescribed a drug

- Switchability refers to the situation where a patient has been stabilized on a particular drug and is then switched to another brand of the same drug.

Therapeutic Equivalence Substitution

- Professional judgment in cases that may affect the substitution of pharmaceutically equivalent products :
  - Excipients
  - Labelling differences: pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary with respect to their expiration time or storage conditions after reconstitution

Conclusion

- Regulatory framework that ensures the safety and efficacy of generic medicines

- Healthcare providers and patient education on safety and efficacy of generic medicines
  - The internet is creating the ”proactive consumer” in healthcare
  - The use of a ‘fear factor’ in misinforming the public should be prevented.

- Positive drug lists - Substitution must be done according to a list specifying the reference listed drug.