Bioequivalence - General Considerations

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Key Output of Programme

- A list of prequalified medicinal products used for treatment of HIV/AIDS, malaria, tuberculosis, influenza, neglected tropical diseases, acute diarrhoea (zinc sulfate), and for reproductive health

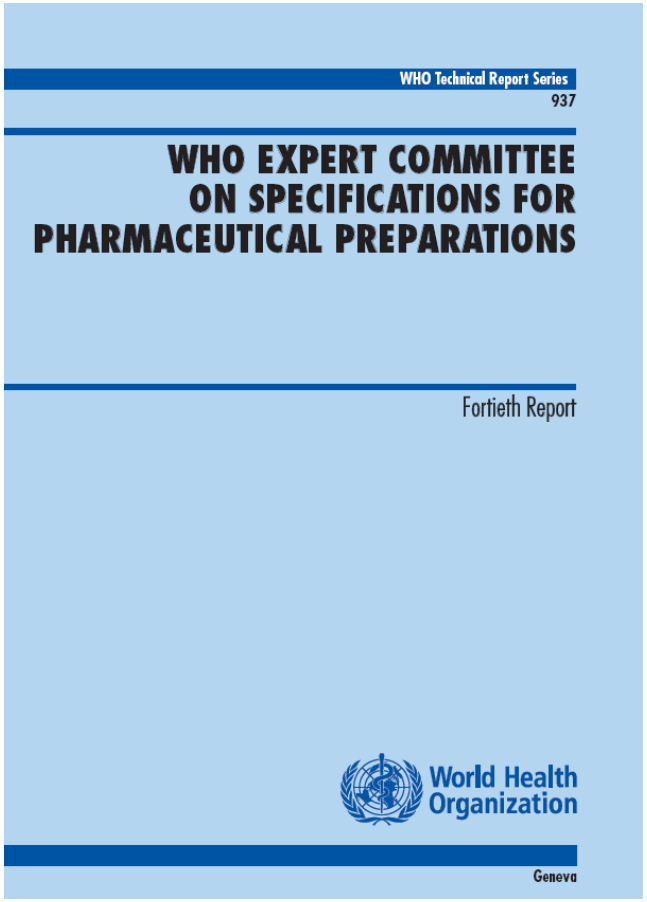
- To get a Finished Pharmaceutical Product (FPP) included on the list, a manufacturer provides a comprehensive set of data about the quality, safety and efficacy of its product
  - Quality Assessment
  - Safety & Efficacy Assessment
  - Product Labeling

Safety & Efficacy

- Most FPPs submitted are multisource (generic) products
  - Abbreviated clinical component
  - Safety & efficacy (S&E) based on comparison to a FPP with established S&E
- Pharmaceutical Equivalence
  - Products are pharmaceutically equivalent if they contain the same molar amount of the same API(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route.

Guidance

"Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7



Pharmaceutical equivalence

– is it enough?

Sometimes, it is …

- Aqueous solutions
  - Intravenous solutions
  - Intramuscular, subcutaneous solutions
  - Oral solutions
  - Otic or ophthalmic solutions
  - Topical preparations
  - Solutions for nasal administration
- Powders for reconstitution as solution

Pharmaceutical Equivalents

Pharmaceutically equivalent FPPs may differ

Differences in formulation

Excipients, drug particle size, mechanism of release

Differences in manufacture

Equipment, process, site

May result in differences in *e.g.,* disintegration and dissolution, and impact product performance

Sometimes, it is not enough

- Pharmaceutical equivalence by itself does not necessarily imply therapeutic equivalence
- Therapeutic equivalence:
  - Pharmaceutically equivalent
  - Same safety and efficacy profiles after administration of same dose

Products that require studies to determine equivalence …

- Solid oral FPPs
  - immediate- and modified-release FPPs
- Complex topical formulations
  - emulsions, suspension, ointments, pastes, foams, gels, sprays, and medical adhesive systems
- Complex parenteral formulations
  - depot injections, nasal/inhalational suspension etc

Establishing Equivalence

- Comparative pharmacokinetic studies
  - *In vivo* comparative bioavailability studies
  - Comparison of performance of FPPs based rate and extent of absorption of API from each formulation
    - Area under the concentration-time curve (AUC)
    - Maximal concentration (Cmax)
    - Time to maximal concentration (Tmax)
- Comparative pharmacodynamic studies
- Comparative clinical trials
- Comparative *in vitro* methods
  - Biopharmaceutics Classification System (BCS)-based biowaivers
  - Additional strengths biowaivers

Bioequivalence

- FPPs are bioequivalent if
  - they are pharmaceutically equivalent or pharmaceutical alternatives
  - bioavailabilities (both rate and extent) after administration in the same molar dose are similar to such a degree that their effects can be expected to be essentially the same

- Pharmaceutical alternative
  - Same molar amount of the same API(s) but differ in dosage form (*e.g.,* tablets *vs.* capsules), and/or chemical form (*e.g.,* different salts, different esters)
  - Deliver the same active moiety by the same route of administration

Establishing Bioequivalence

FPPs being tested

- Comparator product
  - WHO provides recommendations
  - To be discussed shortly
- Test product
  - Biobatch of sufficient size
    - Representative of product proposed for market
    - Support future scale-up
    - Full characterization in dossier

Establishing Bioequivalence

Important PK parameters

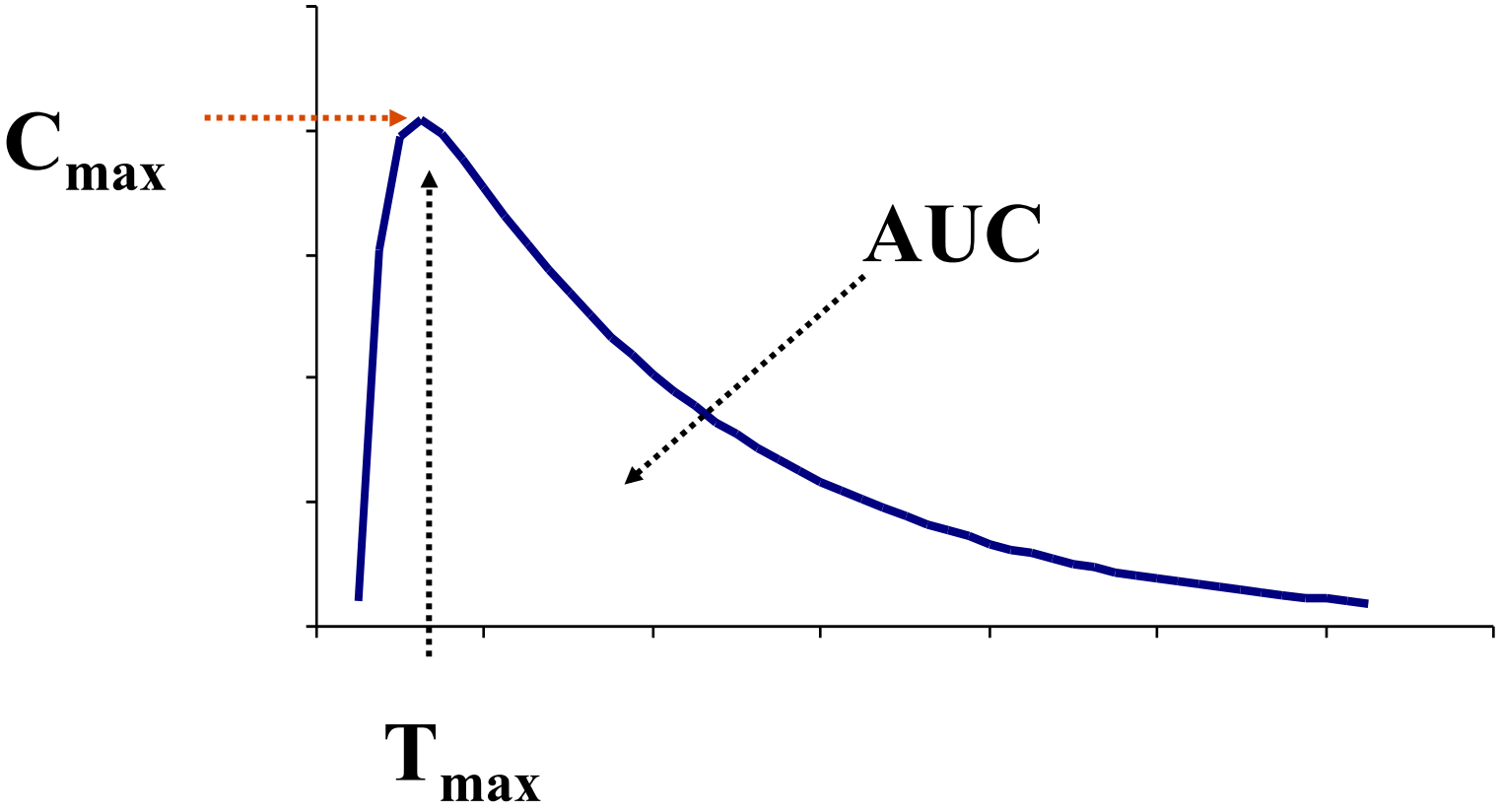
AUC:

area under the concentration-time curve
⇒ measure of the extent of absorption

Cmax:
the observed maximum concentration of a drug
⇒ measure of the rate of absorption

tmax:
time at which Cmax is observed
⇒ measure of the rate of absorption

Plasma concentration time profile



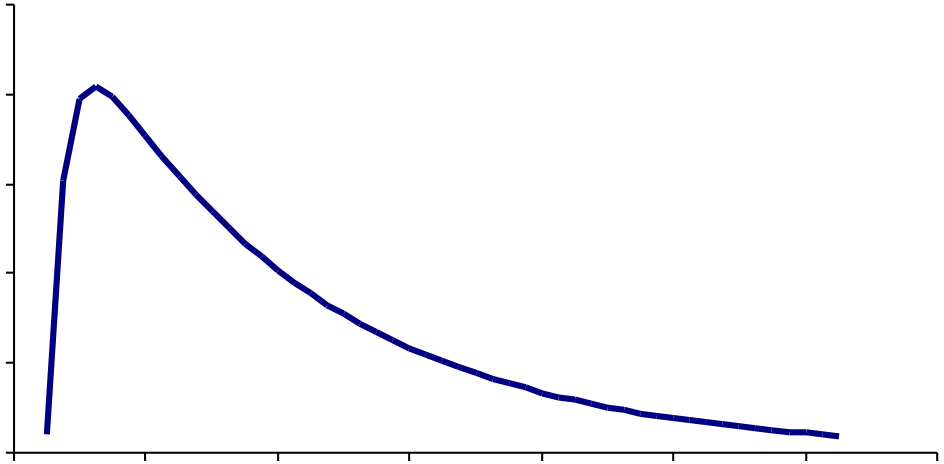
In vivo BE Study Design

Basic design considerations:

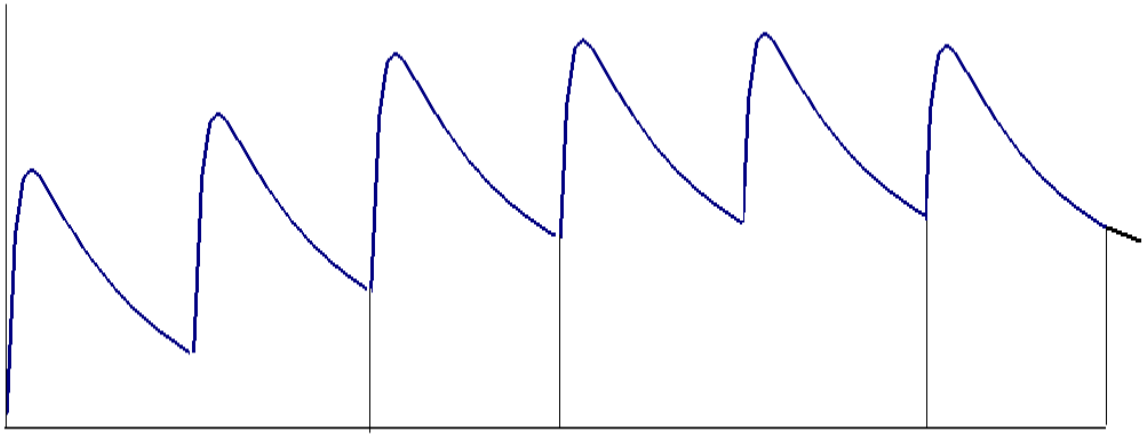
- minimize variability not attributable to formulations
- minimize bias
- goal: compare performance 2 formulations

In vivo BE Study Design

- Single-dose administration



- Multiple-dose administration



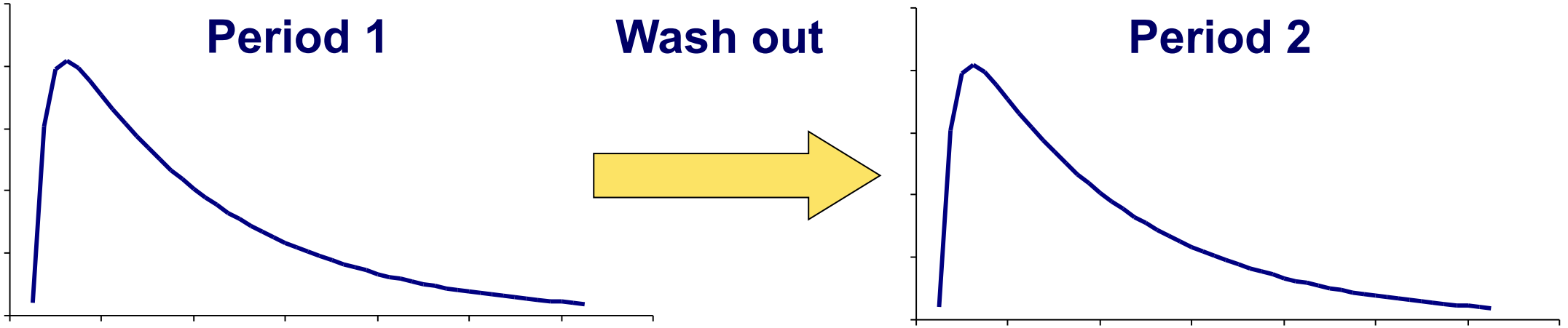
Preferred Approach

- Single-dose design

In vivo BE Study Design

- Crossover Design
  - Each subject administered both test and comparator
  - Within-subject comparison
  - Preferred
- Parallel Design
  - Each subject administered test or comparator
  - Between-subject comparison
  - Only recommended for extremely long half-life drugs
  - Consult WHO

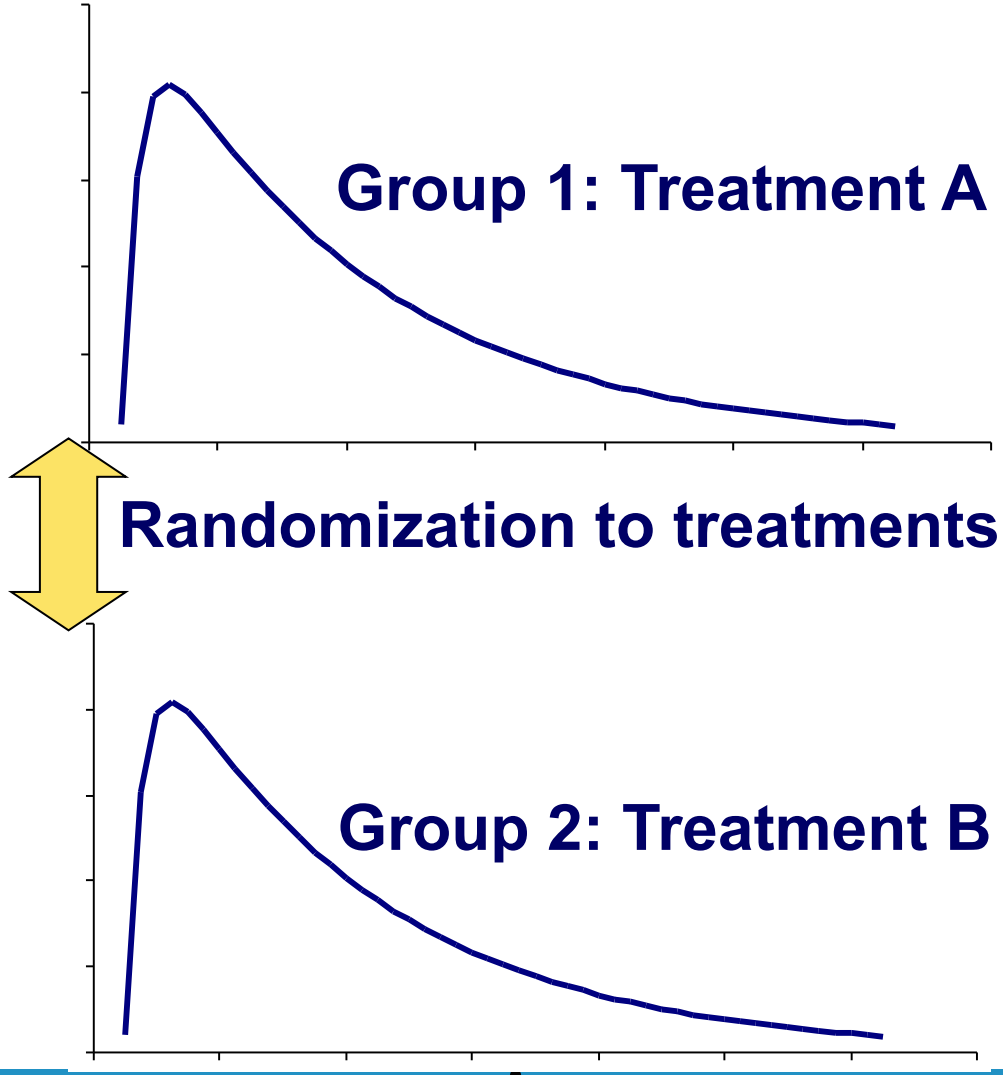
Crossover Design



- Blood samples are collected and assayed
  - Before and several times after drug administration. No need after 72 h
- Prior to period 2, pre-dose levels must be <5% of Cmax of 2nd period
- Wash out period must take into account the slow metabolizers
- Minimum wash out: 7 days (1 week)

Drugs with long elimination $t_{1/2}$: Parallel

- Normally wash-out period should not exceed 3-4 weeks
- If a larger wash-out period is necessary a parallel design may be more appropriate
- Variability will be larger, needs higher sample size
  - Parallel design: Total variability (intra+inter)
  - Cross-over: Intra-subject variability
- Sampling: Up to 72 h



Preferred Approach

- Single-dose administration
- Crossover comparison

Subjects

- Normally healthy volunteers
  - Inclusion / exclusion criteria
  - Randomization
- How many subjects?
  - Required sample size depends on **intra-individual variability** either known through reasonable literature or by means of a pilot study
  - “low” variability: ~ 12 – 26 volunteers
  - “high” variability: ~ can be up to 250 volunteers

Preferred Approach

- Single-dose administration
- Crossover (within-subject) comparison
- Healthy volunteers

In vivo BE Study Design

- Administration of products under fasted or fed conditions?
- Fasted conditions
  - Study conducted under fasted conditions the norm
  - Comparator product labeling (SPC)
    - Specifies fasted conditions
    - Does not specify fasted/fed for administration
    - States that either fasted or fed administration
- Fed conditions
  - If specified in comparator product labeling (SPC)

In vivo BE Study Design

Administration of products under fasted or fed conditions?

- Fed conditions
  - If specified in comparator product labeling (SPC)
  - Type of meal to be consumed
    - high-fat, high-calorie meal
    - "standard" or typical breakfast
- Administration under both fasted **and** fed conditions
  - Not generally necessary for immediate-release products
  - Required for modified-release products

Preferred Approach

- Single-dose administration
- Crossover (within-subject) comparison
- Healthy volunteers
- Administration with or without food
  - Fasted study is the norm
  - Labeling of the comparator product is the guide
    - Bioavailability / pharmacokinetics
    - Adverse events
- Consultation with Programme encouraged

Typical *in vivo* BE Design

- Single-dose administration
- Cross-over (within-subject) comparison
- Healthy volunteers
- Administration with or without food
  - Fasted study is the norm
- Thoroughly validated bioanalytical method
- Data from parent compound used for BE decision
- Analysis should be carried out on the logarithmically transformed AUC_T and C_{max} data

Statistical considerations

Statistical test should take into account…

- **The consumer (patient) risk of erroneously accepting bioequivalence** (primary concern health authorities)

- **Minimize the producer (pharmaceutical company) risk of erroneously rejecting bioequivalence**

Choice:
- two one-side test procedure
- confidence interval ratio T/R 100 (1-2α)
- α set at 5% (90% CI)

Statistical considerations

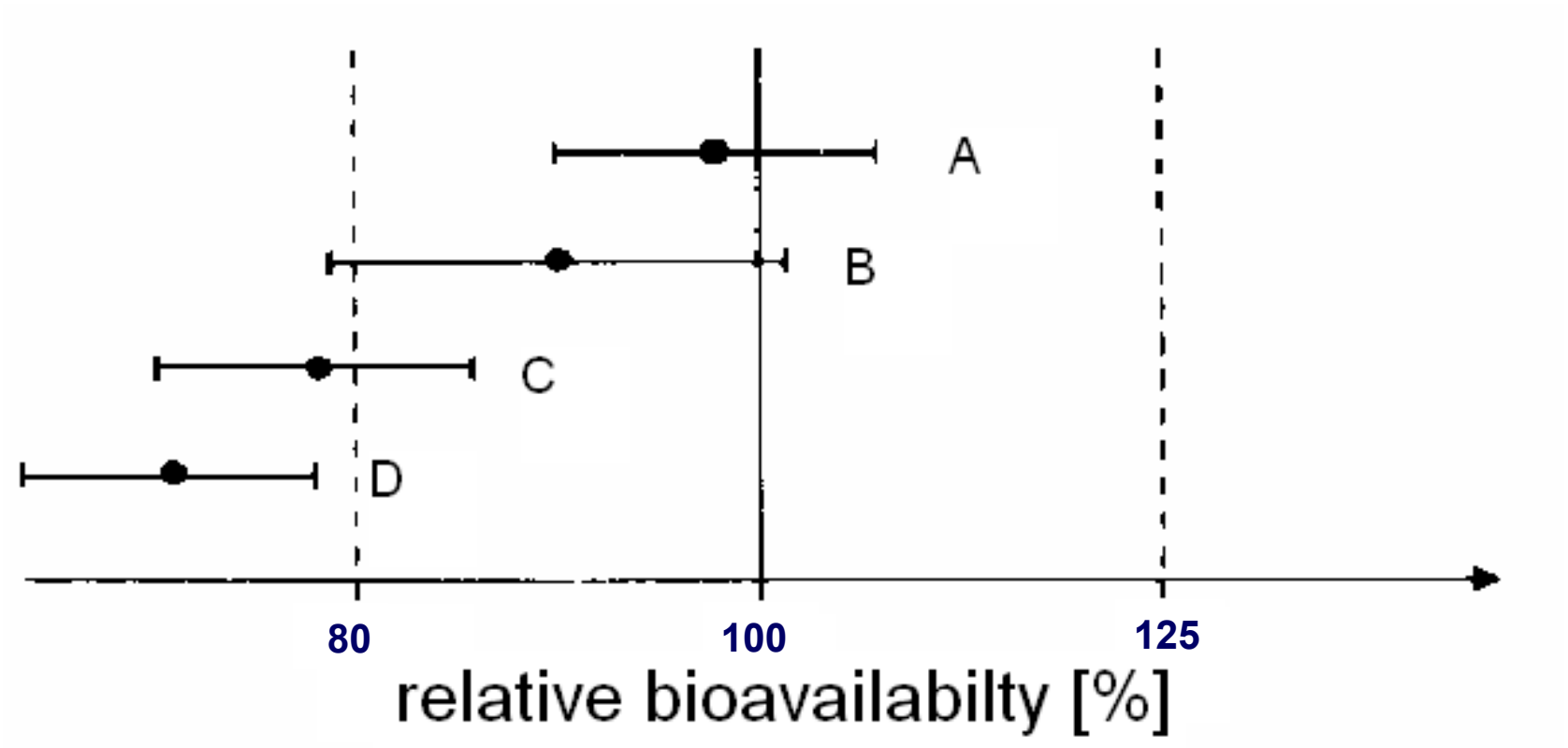
BE Limits

- The concept of the ±20% difference is the basis of BE limits (goal posts)
- If the concentration dependent data were linear, the BE limits would be 80-120%
- On the log scale, the BE limits are 80-125%
- The 90%CI must fit entirely within specified BE limits e.g. 80-125%

Acceptance criteria

- Single-dose, two-way crossover study
- Average bioequivalence
- AUC: 90% Confidence Interval (CI) within 80.0-125.0%
- Cmax: 90% CI within 80.0-125.0%

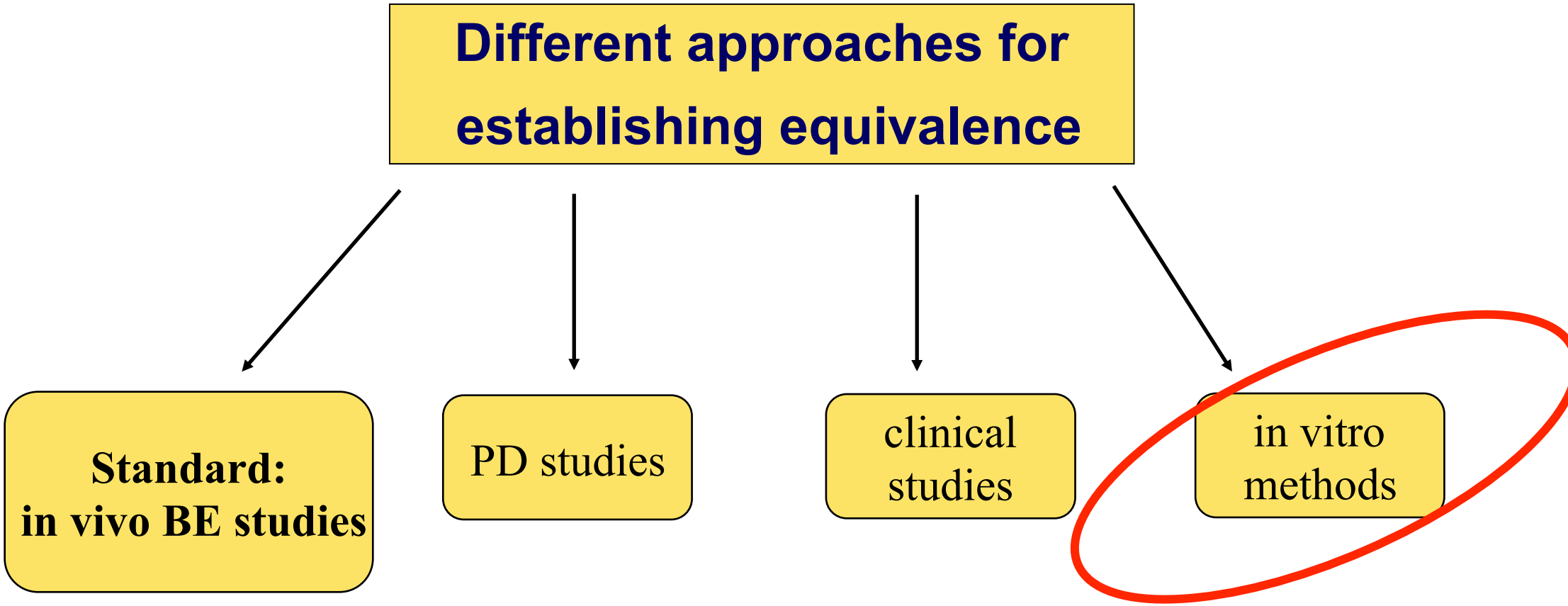
Acceptance criteria



International Comparison

Country/Region	AUC 90% CI Criteria	Cmax 90% CI Criteria
Canada (most drugs)	80 – 125%	none (point estimate only)
Europe & USA	80 – 125%	80 – 125%
South Africa (most drugs)	80 – 125%	75 – 133% (or broader if justified)
Japan (some drugs)	80 – 125%	Some drugs wider than 80 – 125%
Worldwide	80 – 125%	Generally 80 – 125%

Establishing Equivalence



Biopharmaceutics Classification System

- BCS originally explored with the aim of granting biowaivers for scale-up and post-approval changes (SUPAC)
- Biowaiver may be considered when
  - An *in vivo* bioavailability and/or bioequivalence is considered not necessary for FPP approval
    - *In vivo* studies can be expensive and time consuming
  - Under certain circumstances, a dissolution test could be used as a basis for the decision on equivalent product performance
- More recently, further uses of BCS have been explored

Rationale

- The theory is that the oral availability of an API from a FPP can be expected to range from being
  - heavily dependent on the formulation and method of manufacture of the pharmaceutical product (e.g., Class II or IV APIs); to
  - Being mostly dependent on the permeability properties of the API (e.g., Class III APIs)

Rationale

- Requirement for *in vivo* bioequivalence testing may be waived under certain conditions
  - Solubility of API
  - Permeability of API
  - Uncomplicated API
    - Not narrow therapeutic range
    - No known bioavailability problems
  - Immediate-release FPP
  - Acceptable dissolution characteristics of FPP
- Minimizing risk of inappropriate BE decision

Biopharmaceutics Classification System

- Biopharmaceutics Classification System (BCS)
  - Classification system for APIs
    - Aqueous solubility
    - Intestinal permeability
- API classification according to BCS

BCS Classification	Solubility	Permeability
BCS class I	high	high
BCS class II	low	high
BCS class III	high	low
BCS class IV	low	low

BCS-based Biowaiver guidance

- WHO – Technical Report Series No. 937, May 2006

Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms

- FDA - Guidance for Industry: "Waiver of in vivo bio-equivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a Biopharmaceutics Classification System" (2000)

- EMA-guidance: "Guidance on the Investigation of Bioequivalence" CPMP/EWP/QWP/1401/98 Rev.1; Appendix III (2010)

BCS-based Biowaiver

- Eligibility for BCS-based Biowaiver
  - General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications
- Requirements for BCS-based Biowaiver
  - General Notes on BCS-based Biowaiver Applications
  - Biowaiver Application Form: Biopharmaceutics Classification System (BCS)
- http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_implementation.htm

BCS-based Biowaiver: Two step process

1. Classification of the API
   a. Aqueous solubility
   b. Absorption / permeability

2. FPP evaluation
   - Conventional, immediate-release products
   - Comparison to the comparator product
     a. Comparison of formulations (excipients)
     b. Comparative dissolution profiles (CDP)

Step 1

Classification of the API

Classification criteria

High solubility:

- **The highest dose is completely soluble in 250 ml or less of aqueous solution at pH 1.2 – 6.8 (37°C)**

→ 250 ml: derived from typical BE study protocols that prescribe the administration of a FPP to fasting human volunteers with a glass (approximately 250 ml) water

Classification criteria

pH in the gastro-intestinal tract

site	fasted pH	fed pH
stomach	1.4 – 2.1	4.3 – 5.4
small intestine: duodenum jejunum ileum	 4.9 – 6.4 4.4 – 6.6 6.5 – 7.4	 4.2 – 6.1 5.2 – 6.2 6.8 – 7.5
large intestine: cecum upper colon lower colon	 6.4 6.0 7.5	

Classification criteria

High solubility:

- **The highest dose is completely soluble in 250 ml or less of aqueous solution at pH 1.2 – 6.8 (37°C)**

- A solubility profile should be developed
  - At a minimum, solubility should be determined at pH 1.2, 4.5, 6.8, and at pKa if within range

- Dose solubility volume (DSV) = dose (mg) / solubility (mg/mL)

  e.g., highest dose = 500mg, solubility (37°C) at pH 4.5 = 31.2 mg/mL

  DSV = 500/31.2 = 16.03 mL

  16.03mL < 250mL so highly soluble at pH 4.5

Solubility classification for biowaiver eligibility: Based on highest strength or highest dose?

Country/Region	Parameter for solubility classification
Australia Brazil Canada Europe Mexico New Zealand Singapore South Africa Switzerland	Highest therapeutic dose
South Korea USA	Highest strength
WHO PQTm	Highest therapeutic dose

Classification criteria

Highly permeable:

- **An API is considered HIGHLY PERMEABLE when *extent of absorption* in humans is determined to be > 85% of an administered dose, based on a mass balance determination or in comparison to an intravenous reference dose, in the absence of evidence suggesting instability in the gastrointestinal tract.**

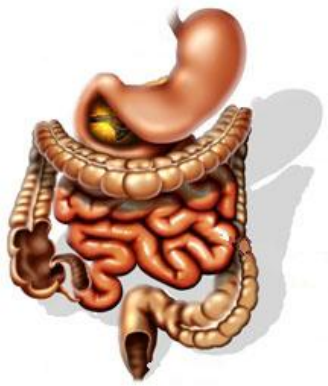
→ Intestinal membrane permeability may be determined by *in vitro* or *in vivo* methods that can predict extent of drug absorption in humans.

Classification criteria

Highly permeable:

- EU guidance: linear and complete ***absorption*** reduces the possibility of an IR FPP influencing the bioavailavility (absorption >85%).

- FDA guidance: absolute bioavailability >90%



Biopharmaceutics Classification System

- Biopharmaceutics Classification System (BCS)
  - Classification system for APIs
    - Aqueous solubility
    - Intestinal permeability
- API classification according to BCS

BCS Classification	Solubility	Permeability
BCS class I	high	high
BCS class II	low	high
BCS class III	high	low
BCS class IV	low	low

Eligibility of an API for a BCS-based biowaiver

1. Classification within BCS
    1. Class I and III APIs are eligible
2. Risk assessment
    1. Narrow therapeutic index (NTI)
    2. Critical use(?)

International Comparison

Country/Region	BCS Class eligible for BW
Europe	I & III
USA	I
Canada	I & III
China Singapore / ASEAN South Korea	I
Brazil	I (only specified APIs)
Japan	None at this time
WHO PQTm	I & III

Current Situation

- Two-pronged approach for biowaiver eligibility
  - APIs identified as Class I or III by PQTm
    - Programme has reviewed existing information on the solubility, bioavailability, and dissolution data of the invited medicines
    - APIs have been identified as eligible for a BCS-based biowaiver application
    - Data for classification not required as part of application
  - Applicants can submit solubility and absorption/permeability data to aid in API classification as part of a biowaiver application

Current Situation

- Medicines for HIV/AIDS and related diseases
  - Abacavir sulfate (Class III)
  - Emtricitabine (Class I)
  - Lamivudine (Class III)
  - Stavudine (Class I)
  - Zidovudine (Class I)

  Related
  - Fluconazole

    polymorphs II & III (Class I)

- NTD treatments
  - Diethylcarbamazine (Class III*)

- Anti-tuberculosis medicines
  - Ethambutol (Class III)
  - Isoniazid (Class III)
  - Levofloxacin (Class I)
  - Moxifloxacin HCl (Class I)
  - Ofloxacin (Class I)
  - Pyrazinamide (Class III)
  - Linezolide (Class I)

Current Situation

- A biowaiver request can be made for monocomponent or fixed-dose combination (FDC) products containing eligible APIs
- Monocomponent or FDC FPPs containing other APIs must be supported with *in vivo* BE data

Step 2

Evaluation of FPP

FPP evaluation

- Selection of comparator product
  - To be discussed
  - Same requirements as comparator for in vivo study
- Biobatch reflective of proposed commercial product
- Two key elements
  - Comparison of formulations (excipients)
  - Comparative dissolution profiles (CDP)

Comparative Dissolution

One component of the evaluation of an FPP

for a biowaiver

What is dissolution testing (IR products)?

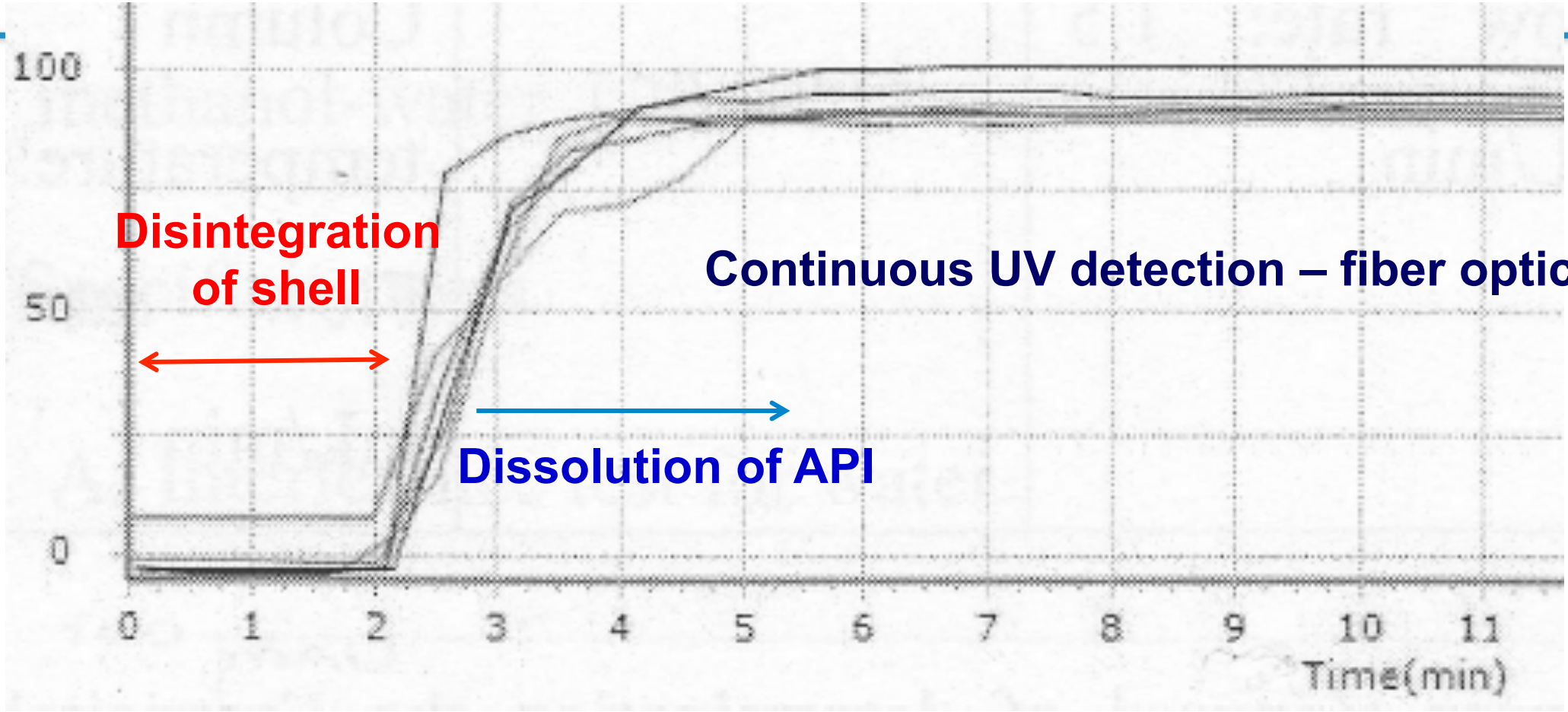
It measures the portion (%) of the API

1. that has been released from tablets/capsules matrix **and**
2. that has dissolved in the dissolution medium during controlled testing conditions within a defined period

In simple terms:

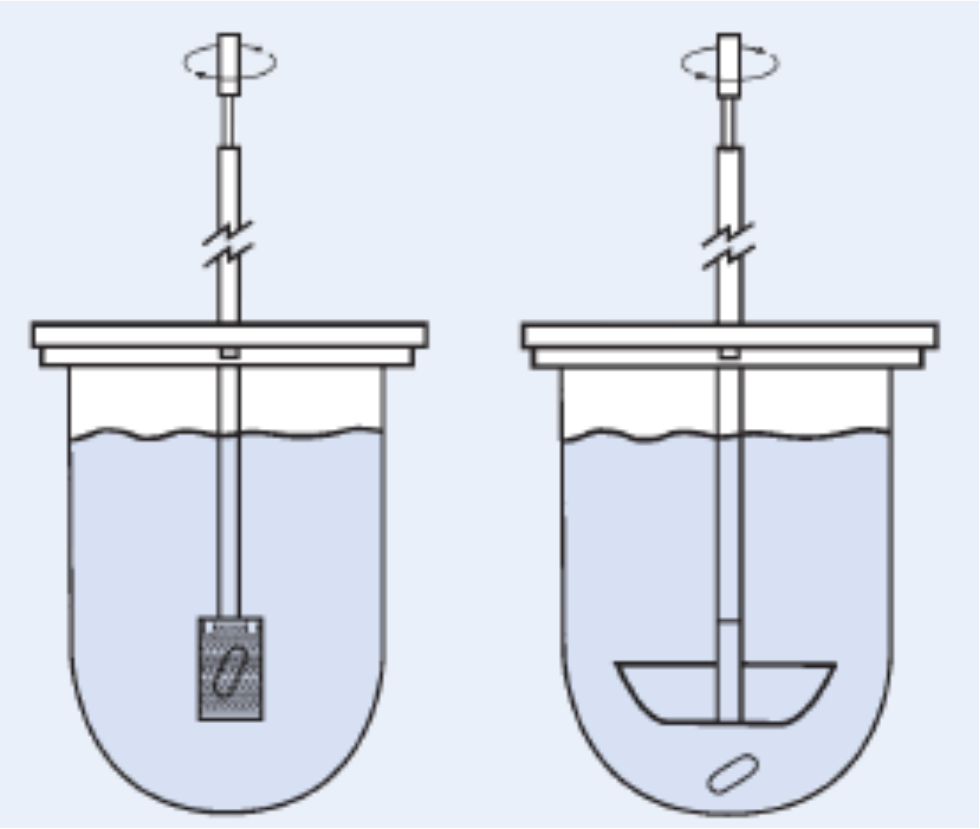
- The tablet/capsule thus first disintegrates
- Then the API will be able to dissolve
- Slow disintegration ➜ slow dissolution

Emtricitabine capsules



Source: Chinese Pharmacopoeial Commission development report

Apparatus



Apparatus 1
basket

Apparatus 2
paddle

Single point dissolution test

- Simplest form of dissolution
  - One sample is withdrawn from the dissolution medium per vessel
    - **Through an in-line or end-of-sampling probe filter**
  - at a pre-determined time point and
  - the sample is analysed for the % API(s) dissolved
    - UV/VIS or HPLC most common

Mostly for FPP release/stability

- Result is given as e.g.
  - 93 % of label claim in 30 minutes (range: 89 – 97 %)
  - No decimal is required

Multi-point dissolution

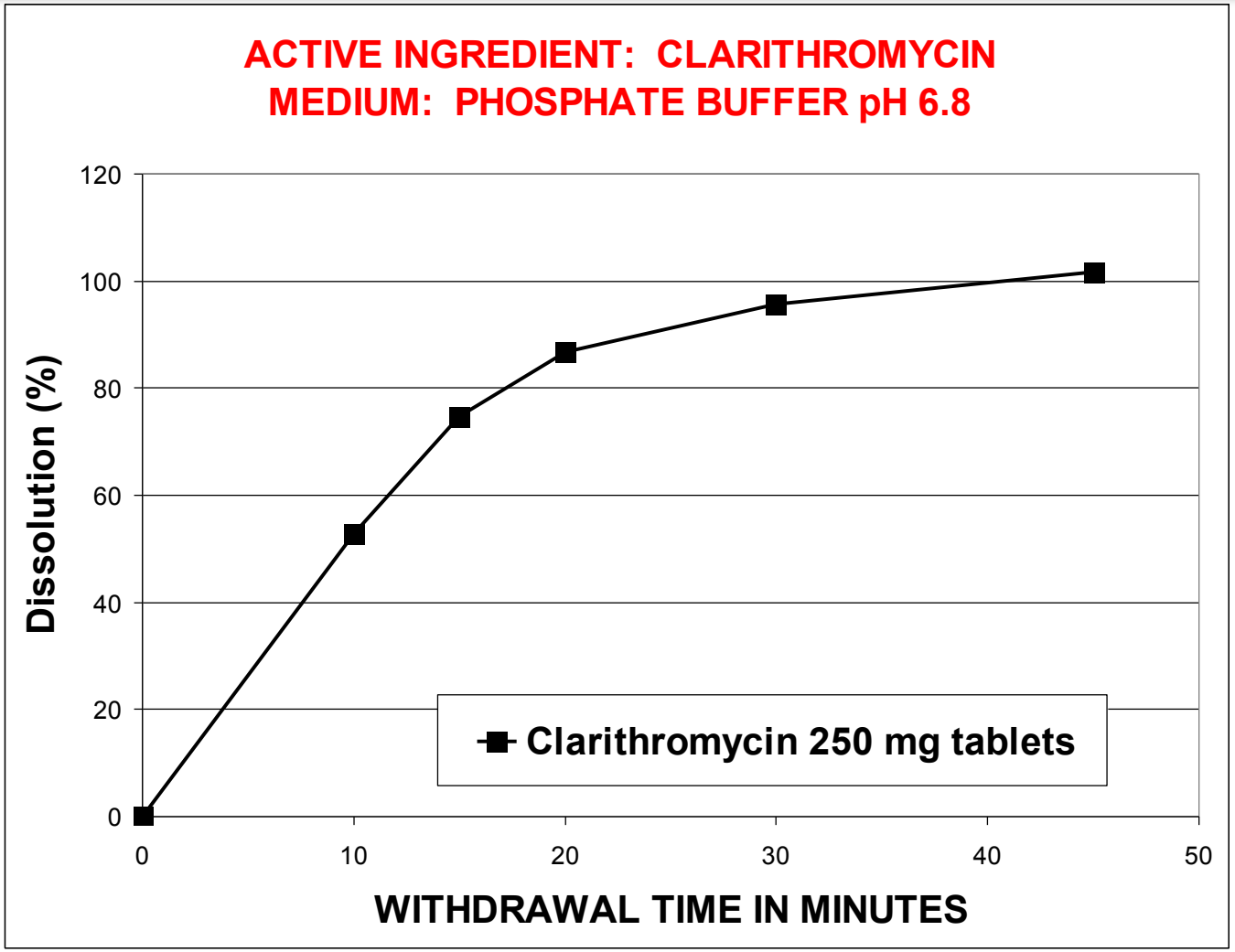
In multipoint dissolution

- multiple (≥ 3) samples are withdrawn from the dissolution medium per vessel during dissolution testing
- at pre-determined time points (intervals) and
- each sample is analysed for the % API dissolved

A graph of % API dissolved against time

= the dissolution profile

Multi-point dissolution
Example of dissolution profile

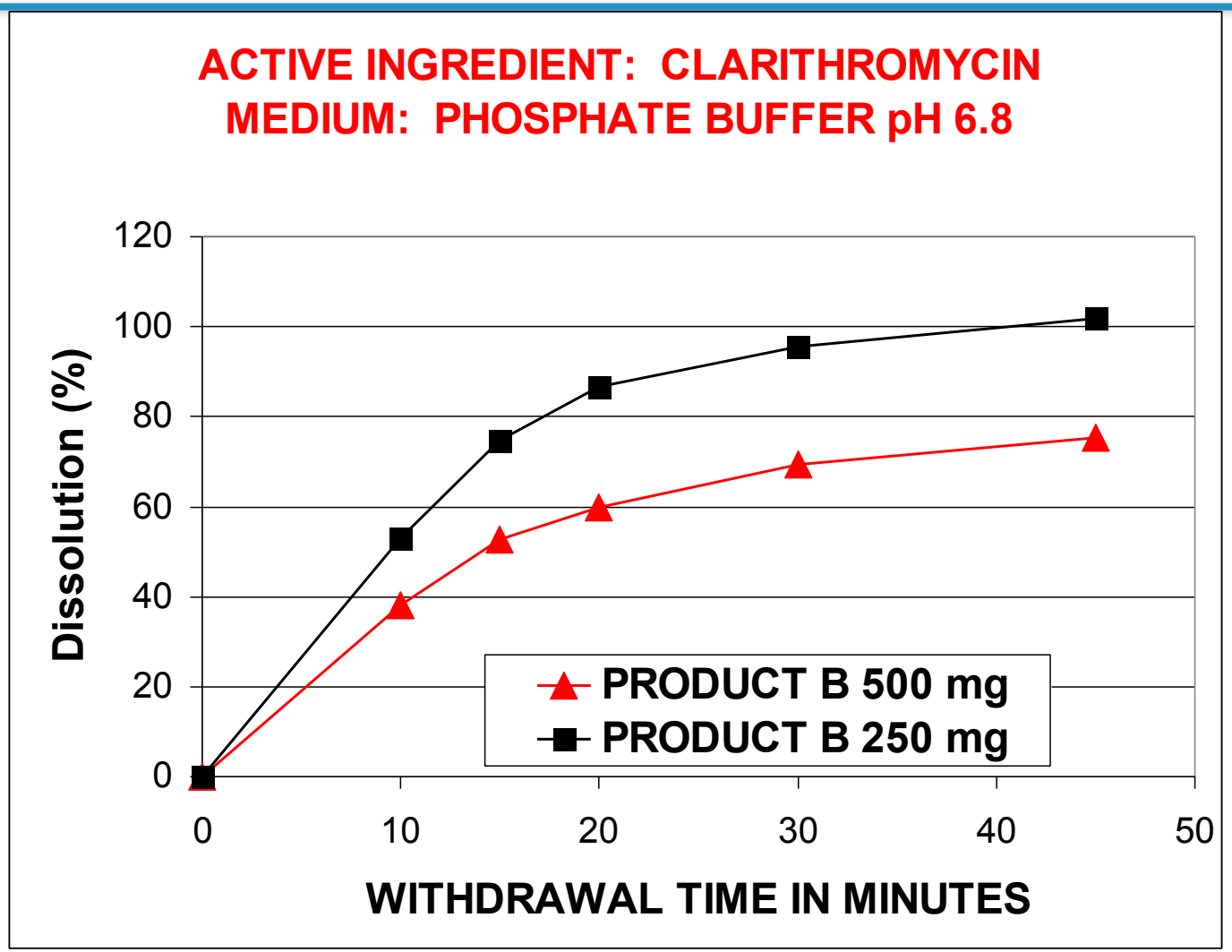


Comparative dissolution testing
The principle and basic requirements

- **Comparison of 2 or more products or batches containing the same API**
  - by means of multipoint dissolution (comparing profiles)

1. The strength of products / batches **may OR may not be the same** depending on purpose of test
2. The dissolution conditions must be the same, e.g.
   - Apparatus, rotation speed, medium, volume & temperature
3. Samples are taken at the **same time points** for data comparison

Comparative dissolution testing Example



Comparative dissolution testing

When are dissolution profiles similar?

Read more: Generic guideline, Appendix 1

- *Recommendations for conducting and assessing comparative dissolution profiles*

Comparative dissolution testing
Profile similarity determination

1. If **both the test and reference product show ≥ 85% dissolution within 15 minutes**,
   - the profiles are considered to be similar
     - No calculations are required

If this is not the case, apply point 2 (next point)

2. **Calculate the f2 value (similarity factor):**
   - If **$f_2 \geq 50$**
     - the profiles are regarded similar
     - No decimal required ($f_2 = 49.51 \equiv 50$)

Comparative dissolution testing
Similarity factor f2

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

n = number of time points

R_t = % API dissolved of reference product at time point x

T_t = % API dissolved of test product at time point x

- Minimum of 3 time points (zero excluded)
- 12 units (one / vessel) for each batch
- Only one measurement should be considered after the reference product has reached 85 % dissolution (or asymptote is reached)
- RSD: ≤ 20% at early time point &
  ≤ 10% at later time points (apply with some discretion)

Typical mistakes

Often manufacturers include the following points in the f2 calculation

- **Time zero** in the f2 calculation
  - % dissolved = 0 at t = 0 minutes
- Points **beyond** the reference product reaches **85%**

  It is not according to the "rules"
- What is the problem with including these points?

  The f2 value will increase – **may lead to false positive f2**

Comparative dissolution testing
Similarity factor f2

Take note - **apply WHO requirement in PQP**:

- Unfortunate differences between WHO, FDA and EMEA guidelines on determination of "dissolution last point" for f2 calculations:

Source	Only one measurement (of both products) should be considered after:
FDA (2000)	BOTH the reference AND test products have reached 85 % dissolution (or asymptote is reached)
WHO (2006)	the REFERENCE product has reached 85 % dissolution (or asymptote is reached)
EMEA (2010)	ANY ONE of the reference OR test product has reached 85 % dissolution (or asymptote is reached)

Comparative dissolution testing
Dissolution conditions (study design)

Apparatus (choice)	• Paddle, 75 (or 50) rpm or • Basket, 100 rpm
Dissolution media (All three media for full comparison)	1. pH 6.8 phosphate buffer 2. pH 4.5 acetate buffer 3. Buffer pH 1.2 or 0.1 M HCl 4. Release medium (if different)
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	5,10, 15, 20, 30, 45, (60, 120) min. (short intervals)
Units (vessels)	12

Comparative dissolution testing
Comparison of products / batches

When are the dissolution properties of two products (batches) regarded similar?

When their dissolution profiles are similar

- in all media (not so simple for Class 2 and 4 APIs)

- Statements of instability or insolubility are not acceptable unless demonstrated / justified (literature also acceptable)
  - Assessor must query unjustified statements like this

FPP evaluation (Back to it!)

- Selection of comparator product
  - To be discussed
- Biobatch reflective of proposed commercial product
- Two key elements
  - Comparison of formulations (excipients)
  - Comparative dissolution profiles (CDP)

Dissolution test conditions

- Comparative *in vitro* dissolution
  - Comparative testing should ensure the similarity of the test and comparator product in three different pH media considered relevant for absorption from the GI tract
  - Comparative *in vitro* dissolution testing should be conducted in at least three aqueous media of pH 1.2, 4.5, and 6.8
    - Volume of media: 900 mL
    - Temperature of media: 37 ± 1°C
    - Agitation: paddle apparatus at 75 rpm or basket apparatus at 100 rpm
    - Replicates: 12 units
    - Sampling schedule: *e.g.*, 5, 10, 15, 20, 30, and 45 minutes
    - Surfactants not permitted

Dissolution Definitions

- ‘Very rapidly’ dissolving FPPs
  - Not less than 85% of the labeled amount is released within 15 minutes or less from the test and comparator product
  - In this case, profile comparison is not needed
- ‘Rapidly’ dissolving FPPs
  - Not less than 85% of the labeled amount is released within 30 minutes or less from the test and comparator product
  - Profile comparison (*e.g.,* f2 testing) required

FPP comparison
Class I APIs

- Excipients
  - Should employ well known excipients in usual amounts
  - Beneficial to contain similar amounts of the same excipients
  - Critical excipients (*e.g.,* mannitol, sorbitol, surfactants), if present, should not differ qualitatively or quantitatively

- Comparative *in vitro* dissolution
  - Products should be similarly rapidly dissolving
    - NLT 85% in 30 minutes for both products
    - f2 profile comparison (unless 85% in 15 minutes for both FPPs)

FPP comparison
Class III APIs

- APIs are highly soluble but limitations to absorption due to various reasons

- Excipients
  - Qualitatively the same excipients
  - Quantitatively very similar (as per Level 1 change according to SUPAC)

- Comparative *in vitro* dissolution
  - NLT 85% dissolved within 15 minutes for both products

Considerations

- BCS-based biowaivers for some FDCs difficult
  - FDC comparator not available
- FDCs must include only Class I or III APIs to be eligible *e.g.,* rifampicin containing FPPs are not eligible for a BCS-based biowaiver
- Identification of API eligibility based on solubility, permeability, safety and related properties
  - This does not imply that the comparator product(s) will be very rapidly or rapidly dissolving
  - Very rapidly or rapidly dissolving properties are not required to make an *in vivo* bioequivalence comparison

Considerations

- The comparative *in vitro* dissolution data is the equivalence data
  - Fully developed protocol and operating procedures
  - Complete documentation
  - Biowaiver Application Form: Biopharmaceutics Classification System
  - Monitoring, auditing, inspection

BCS-based biowaiver
Fictional example

- Refer to handout
- Step 1: Classification of API
  - Two-pronged approach for PQTm
    - 1. PQP identifies eligible APIs
      - Solubility data in dossier should corroborate classification
    - 2. Applicant provides classification data

BCS-based biowaiver
Fictional example

- Step 2: FPP evaluation
  - Biobatch assessment
  - Comparative assessment of formulation
    - Proposed product
    - WHO comparator product
  - Comparative dissolution profiles
    - At a minimum, at pH 1.2, 4.5, and 6.8
- Conclusion of assessment
  - Biowaiver granted?
  - Next steps

Additional strengths biowaivers

- Waiver of requirement to conduct *in vivo* BE studies with each strength of a product line
- *In vivo* data available for one strength
  - Usually highest strength
  - Linear pharmacokinetics
- Similarity of formulations
  - Proportionality
- Similarity of dissolution characteristics

Similarity of formulations

- Annex 7 of TRS 937 defines proportionally similar formulations as:
- All active and inactive ingredients are in exactly the same proportion in the different strengths
  - e.g., 50 mg tablet has exactly half of all ingredients of 100 mg tablet and twice that of 25 mg tablet
- For a high potency API (amount of API is low; up to 10 mg per dosage unit)
  - Total weight of FPP remains the same (within ± 10%)
  - Same inactive ingredients, change obtained by altering API with corresponding change to the highest percentage excipient

Similarity of dissolution characteristics

- Comparative *in vitro* dissolution testing
  - Comparative testing should ensure the similarity of the different strengths in three different pH media considered relevant for absorption from the GI tract
  - Comparison of different strengths within product line
  - Not comparison to comparator product
    - Comparison to comparator may be supportive in some cases *e.g.*, Class IV API

Comparative *in vitro* dissolution

- Immediate-release FPPs
  - Comparative testing should be conducted in at least three media of pH 1.2, 4.5, and 6.8
  - 12 units
  - Paddle apparatus at 75 rpm or basket apparatus at 100 rpm
  - Use of surfactants discouraged
  - If both strengths release >85% in 15 minutes, further profile comparison unnecessary
  - Otherwise, profile comparison required
    - f2 testing

Comparator (Reference) Products

- A FPP with which the multi-source product is intended to be interchangeable in clinical practice
- The selection of the comparator product is usually made at the national level by the drug regulatory authority
- A different set of circumstances apply to comparator selection for Prequalification Programme (PQP)

Comparator (Reference) Products

Example of how a national RA can select a comparator:

- choose innovator for which quality, safety and efficacy has been established from national market (nationally authorised innovator)
- choose WHO comparator product from the comparator list (WHO comparator product)
- choose innovator product from well-regulated country (ICH et al. innovator)
- if no innovator comparator is available, a generic market leader can be chosen

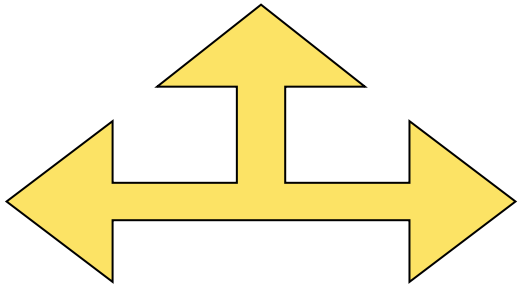
Comparator (Reference) Products

Selection of a comparator for a single national market:

→ **Difficult to translate when other countries are at stake**

→ **National comparator may be the national market leader**

No problem in that market



but others!?

EMA (Europe)

Differentiate between use for single market or many countries!

EMA:

For an abridged application claiming essential similarity to a reference product, application to numerous Member States based on bioequivalence with a reference product from one Member State can be made.

Prequalification program

Comparator (Reference) Products

- Comparator products should be obtained from a well regulated market with stringent regulatory authority *i.e.,* from countries participating in the International Conference on Harmonization (ICH)

- Countries officially participating in ICH
  - ICH members: European Union, Japan, USA, Canada, and Switzerland
  - Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.

Comparator lists

- List of acceptable comparator products for each treatment area on WHO PQP website
- http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_comparator.htm
- There are instances when a comparator is not available in the ICH region
  - *e.g.,* Terizidone 300mg
    - Terivalidin 250 mg (Sanofi-Aventis, South Africa)
  - *e.g.,* Artesunate + Amodiaquine 100 mg + 270 mg FDC
    - Coarsucam (Sanofi-Aventis)

Recommended comparator products: anti-tuberculosis medicines

Invited medicinal products	Recommended comparator product (Strength, Manufacturer)
Single ingredient first-line anti-tuberculosis medicines	
Ethambutol, 100 mg tablet and 200 mg, 275 mg and 400 mg tablet/capsule, 25 mg/ml oral solution	Myambutol (400 mg tablet, Riemser Arzneimittel or Teopharma) Ethambutol hydrochloride (100, 400 mg tablet, West Ward, US[2])
Isoniazid, 50 mg, 100 mg and 150 mg tablet and 300 mg tablet/capsule	Isozid (100 mg tablet, Fatol) Isoniazid (100 mg, 300 mg tablet, Sandoz, US[2])
Pyrazinamide, 150 mg tablet and 250 mg and 400 mg tablet/capsule, 30 mg/ml oral syrup	Pyrazinamide Lederle (500 mg tablet, Riemser Arzneimittel) Pyrazinamide (500 mg tablet, Dava Pharms Inc, US[2])
Rifampicin, 150 mg and 300 mg capsule	Rimactane (150 mg, 300 mg tablet, Novartis or Sandoz) Rifadin (150 mg, 300 mg capsule, Sanofi-Aventis) Rifampicin (150mg, 300 mg, Sandoz, NL)
Streptomycin, 0.75 g and 1 g powder for solution for injection (vial)	Streptomycin (1g/2.5ml injection, Pfizer, US[2])
Fixed-dose combination products of first-line anti-tuberculosis medicines:	
Isoniazid + Rifampicin, 75 mg + 150mg, 150 mg + 150 mg, and 150 mg + 300 mg tablet/capsule	Rifinah (rifampicin 300 mg + isoniazid 150 mg tablet, Sanofi-Aventis), Rifamate (rifampicin 300 mg + isoniazid 150 mg capsule, Sanofi-Aventis, US[2])
For other invited fixed-dose combination products of anti-tuberculosis medicines, use appropriate combination of the recommended single ingredient comparator products	

Comparator (Reference) Products

Information Requirements

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme

Summary

- Study design considerations for *in vivo* bioequivalence studies
- *In vitro* approaches for establishing bioequivalence
  - BCS-based biowaivers
  - Additional strengths biowaivers
- Key elements for comparative dissolution testing
- Selection of comparator products

Thank you for your attention!