An Introduction to Bioequivalence Studies

BCS Classification

F-MRI- LU

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OUTLINE

• Definitions
• Introduction to Pharmaceutical and Therapeutic Equivalence
• Bioequivalence studies:
  • Parameters
  • Different Designs
  • Considerations
• In-vitro testing
• Bio waivers
• BCS Classification
  • Definition
  • Impact on: Bio waivers and Drug Development
History. One of the medicine's most celebrated clinical trials.

Wood engraving from 1885 showing a young patient receiving an anti-rabies vaccine developed by Louis Pasteur. A physician administers the vaccine while Pasteur, a chemist, looks on.
Definitions

**Contract Research organization (CRO):**
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in written agreements.
Definitions

*Good Clinical Practice (GCP)*: A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies,

and which ensures that the studies are scientifically and ethically sound

and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.
Definitions

Good Laboratory Practice (GLP)*: A quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported as applied to human bioanalysis studies
Definitions

Bioavailability
The rate and extent to which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.”

Reference:
intravenous administration = 100% bioavailability

When we talk about bioavailability, we must distinguish between absolute and relative bioavailability
The absolute bioavailability for a given drug from a dosage form is the fraction of the administered dose which is absorbed intact into the systemic circulation.

This is measured by comparing the amount of intact drug that reaches the systemic circulation after extravascular (e.g. oral or intramuscular) administration of a known dose with the amount of intact drug that reaches the systemic circulation after administration of a known dose in the form of an intravenous dose (100% bioavailability).
Bioavailability

- Absolute bioavailability (F):

\[
F = \frac{AUC_{extravascular}}{AUC_{intravenous}} \times \frac{Dose_{intravenous}}{Dose_{extravascular}}
\]
The relative bioavailability

In case of relative bioavailability, the bioavailability of a given drug from an extravascular dosage form is compared to the bioavailability of the same drug administered in another extravascular dosage form.

Hence, relative bioavailability measurements can be used to determine the effects of dosage form differences on the systemic bioavailability of a given drug.
Bioavailability

- Relative bioavailability ($F_{rel}$)

$$F_{rel} = \frac{\text{AUC}}{\text{AUC}_{\text{extravascular1}}} \times \frac{\text{Dose}}{\text{Dose}_{\text{extravascular2}}}$$
Bioequivalence studies

- Bioequivalence is an extension of the concept of relative bioavailability, which essentially involves comparing the bioavailability of a particular drug from a test dosage form (Copy) and a recognised standard dosage form (innovator product).

Products impacted usually are generics (Multi source products)

- Therapeutic equivalence is generally demonstrated by bioequivalence studies conducted in certified CRO’s
Introduction
Pharmaceutical equivalence of Two products

• Same amount of the same active pharmaceutical ingredient
  • Salts, esters
• Same dosage form
  • Comparable dosage forms
  • e.g., tablet vs. capsule
• Same route of administration

• *Is pharmaceutical equivalence enough?*
• *How can we establish therapeutic equivalence and interchangeability*
To Grant Market authorization to a Generic

• Demonstration of equivalence to the innovator reference (comparator) product implies
  • Interchangeability
  • Therapeutic equivalence
Sometimes pharmaceutical equivalence is enough

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

HOWEVER

Two products that are considered pharmaceutically equivalents can still differ to such an extent that it will influence the product performance in vivo, which may make the two products bioinequivalent. Possible differences include:

• Drug particle size (especially important for poorly soluble drugs)
• Excipients (can influence both solubility and permeability of the active ingredient)
• Manufacturing Equipment or Process (e.g. differences in blending time, differences in granulation method)
• Site of manufacture (same product manufactured at different sites within the same company)
Pharmaceutical Equivalents

Possible Differences
- Drug particle size
- Excipients
- Manufacturing Equipment or Process
- Site of manufacture

Could lead to differences in product performance \textit{in vivo}
Sometimes pharmaceutical equivalence 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
Marketing authorization through equivalence

• Suitable methods for assessing equivalence:
  • Comparative pharmacokinetic studies: BE studies
  • Comparative pharmacodynamic studies
  • Comparative clinical trials
  • Comparative in vitro tests
Bioequivalence Studies
When are bioequivalence studies employed?

• Multisource product or GENERIC vs. Innovative product

• Pre-approval changes
  • Bridging studies

• Post-approval changes

• Additional strengths of existing product

(According to ICH E5 guideline, a bridging study on a medicine can be defined as an additional study executed in the new region to "build a bridge" with the foreign clinical data on safety, efficacy, and dose response. This bridging of clinical studies is usually made by allowing extrapolation of the foreign clinical trial data to the population in the new region.)
BE Designs

• BE studies are designed to compare the \textit{in vivo} performance of multisource product with that of the innovator

• Two purposes:
  • Provide in vivo measure of pharmaceutical quality
  • Surrogate of clinical proof of equivalence

• It is necessary:
  • To minimize variability (within and between subjects)
  • Eliminate bias (unequal carry-over effect in 2x2 designs)

• \textbf{REMEMBER}: The Main goal is to compare pharmacokinetics performance of the two products
Pharmacokinetic Parameters

- **AUC**: area under the concentration-time curve ⇒ measure of the extent of bioavailability
- **$C_{\text{max}}$**: the observed maximum concentration of drug ⇒ measure of both the rate of absorption and the extent of bioavailability
- **$t_{\text{max}}$**: the time after administration of drug at which $C_{\text{max}}$ is observed ⇒ measure of the rate of absorption

Note that bioequivalence standards are applied to the pharmacokinetic parameters AUC and Cmax but not to $T_{\text{max}}$. 
Plasma concentration time profile

This is an example of a plasma concentration time profile following extravascular administration of a drug. The parameters often used in bioequivalence assessments are here marked as AUC, $C_{\text{max}}$, and $T_{\text{max}}$. 

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Acceptance range for bioequivalence testing

- CI 90%
- AUC and Cmax: 80 – 125%
“Golden Standard” Study Design

- Single-dose, two-period, crossover
- Healthy volunteers
- Subjects receive each formulation once
- Adequate washout
Conventional Design: 2x2 Cross-Over

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**Randomization to sequences of treatment**

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<thead>
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<th>Period 1</th>
<th>Washout (passive)</th>
<th>Period 2</th>
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<tbody>
<tr>
<td>Sequence 1 (AB) (n subjects)</td>
<td>Innovator product</td>
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<td>Multisource product</td>
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<tr>
<td>Sequence 2 (BA) (n subjects)</td>
<td>Multisource product</td>
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<td>Comparator product</td>
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A two-period, two sequence, single dose, cross-over, randomized design in healthy volunteers
Wash-out to avoid carry-over

- Blood samples are collected and assayed
  - Before and several times after drug administration.
  - Max 72 hours
- 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)
Alternative designs: Multiple dose

- Drug is too potent/toxic for administration in healthy volunteers
  - Patients / no interruption of therapy
- Extended/modified release products
  - Accumulation using recommended dosing interval
  - In addition to single-dose studies
- Non-linear pharmacokinetics at steady-state (e.g., saturable metabolism)
- Analytical method not sufficiently sensitive for single-dose study
Alternative designs: Multiple dose

• In the past a multiple dose study was required in EU for drugs that exhibit non-linear kinetics at steady state (e.g. saturable metabolism, active secretion)
  • No longer required in EU
  • Included in WHO guideline
• Extended release dosage-forms with a tendency to accumulation
  • In addition to single dose studies
    • Fasted state
    • Fed state
Drugs with long elimination $t_{1/2}$: Parallel Design

- 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 hours
Crossover vs. Parallel Designs

- Crossover design preferred
  - Intra-subject comparison
  - Lower variability
  - Generally fewer subjects required
- Parallel design may be useful
  - Drug with very long half-life
  - Crossover design not practical
## Replicate Designs

- Typically four-period design
  - Each product administered twice
- Intra-subject variability
- Subject X formulation interaction
- Different approaches possible
  - Average bioequivalence
  - Individual bioequivalence

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Replicate Designs

- Advantages
  - More information available
  - Different approaches to assessment are possible

- Disadvantages
  - Bigger commitment for volunteers
  - More administrations to healthy volunteers
  - More expensive to conduct
Sampling times

- Blood samples with frequency sufficient frequency for assessing Cmax, AUC and other parameters
- Sampling points should include:
  - a pre-dose sample,
  - at least 1–2 points before Cmax,
  - 2 points around Cmax and
  - 3–4 points during the elimination phase.
- Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters.
Sampling times- Additional considerations

• For most medicines, the number of samples necessary will be higher to compensate for inter-subject differences in absorption and elimination rate, and thus enable accurate determination of the maximum concentration of the API in the blood (Cmax) and terminal elimination rate constant in all subjects.

• Generally, sampling should continue for long enough to ensure that 80% of the AUC (0→ infinity) can be accrued, but it is not necessary to sample for more than 72 hours.

• The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.
Considerations
Fast and Fed conditions

• Immediate Release Formulations
• Modified Release Formulations
Immediate release:
Fasting or fed conditions

- Fasted-state studies are generally preferred
  - Labelling only on an empty stomach, or
  - Labelling irrespective of food intake
- Fed state:
  - When the product is known to cause gastrointestinal disturbances in the fasted state, or
  - If labelling restricts administration in the fed state
- Composition of meal may depend on local diet and customs
Fasting conditions

- Overnight fast of at least 10 hours
- Participants are allowed free access to water
- No water is allowed during the hour prior to drug admin.
- The dose should be taken with a standard volume of water
  - Usually 150–250 ml.
- 2 h after drug admin. water is again permitted ad libitum.
- A standard meal is usually provided 4 hours after drug ad.
Additional requirements in EU

EMA (2010):

• For products with specific formulation characteristics
  • microemulsions,
  • solid dispersions, …

BE studies performed under both fasted and fed conditions are required.
Unless the product must be taken only in the fasted state or only in the fed state
Additional requirements in US-FDA

- In addition to a BE study under fasting conditions, BE study under fed conditions are required for all orally administered immediate-release drug products.
- Except:
  - When both test product and reference product are rapidly dissolving, have similar dissolution profiles, and contain a BCS Class I drug substance,
  - When the label states that the product should be taken only on an empty stomach, or
  - When the label does not make any statements about the effect of food on absorption or administration.
Fed conditions: meal composition

- In studies performed under fed conditions, the composition of the meal is recommended to be according to the SPC of the originator product
- The composition of the meal may depend on local diet and customs
- If no specific recommendation is given in the originator SPC, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 Kcal) meal

- SPC: Summary of Product Characteristics
Meal composition in Fed conditions

- The test meal should derive approximately
  150 Kcal from Protein
  250 Kcal from Carbohydrates
  500-600 Kcal from Fat
- The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).
Considerations for Modified Release Products

• Types:
  • Single-unit formulations
  • Multiple-unit formulations

• Proportional formulations
  • Multiple-unit formulations: testing highest strength is enough. The other proportional strengths are waived based on dissolution
Considerations for Modified Release Products

• Types:
  • Prolonged release: sustained-, controlled-, extended-release
  • Delayed release: gastro-resistant

• Several studies are required:
  • Single-dose fasted-state cross-over with highest strength
  • Single-dose fed-state cross-over with highest strength
    • High-fat meal (time according to SPC or 30 min before drug intake)
  • Multiple-dose fasted state for prolonged release product with a tendency to accumulate (not in FDA)
  • *In vitro* dissolution studies on alcohol effect (10, 20, 40%)
Considerations for Modified Release Products

- Single-unit formulations:
  - US-FDA: BE with the highest strength is enough
    Dissolution at least three media (e.g., pH 1.2, 4.5 and 6.8)
  - EU: All strengths have to be tested in the fasted-state
    single-dose study
    - Highest strength in fed-state single-dose or fasted-state
      multiple-dose
Fasted vs. Fed Designs

• Fasted study design preferred
  • Minimize variability not attributable to formulation
  • Better able to detect formulation differences
• Fed conditions depend on local diet and customs
  • Avoiding GI disturbance
    • Minimal meal to minimize impact
  • Required due to drug substance / dosage form
    • Modified-release products
    • Complicated pharmacokinetics
  • Known effect of food on drug substance
Comparative *in vitro* Studies

- May be suitable *in lieu* of *in vivo* studies under certain circumstances
- Requirements for waiver (to be discussed later)
In vitro testing

- Over the past three decades, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products.
- The dissolution test ... is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) a comparative in vitro dissolution profile similarity can be used to document equivalence of a multisource with a comparator product.
Comparative Dissolution profile …

When the multisource test and the reference products both dissolve with sufficient rapidity (e.g. >80% in 15 minutes) their in vivo equivalence may be presumed. Approval of multisource formulations by the use of comparative in vitro dissolution studies should be based on the generation of comparative dissolution profiles rather than single-point dissolution tests … Multiple dissolution test conditions and physiologically relevant media are recommended.
Biowaiver

A “biowaiver” is an exemption from conducting human bioequivalence studies when the active ingredient(s) meet certain solubility and permeability criteria in vitro and when the dissolution profile of the dosage form meets the requirements for an "immediate" release dosage form.
Waiver of In Vivo Bioequivalence Study are based on

- **Pharmaceutical Dosage Form (Solutions)**
- **Dose.** (Highest Strength should be tested)
- **Biopharmaceutics Classification System (BCS)**
Biopharmaceutics Classification System

Guidance provided for predicting the intestinal drug absorption

- The fundamental basis established by Dr. Gordon Amidon

First introduced into regulatory decision-making process in the FDA guidance document on Immediate Release Solid Oral Dosage Forms:

Scale Up And Post Approval Changes
BSC based bio-waiver: a long way from concept to practice

- **1995 FDA** – SUPAC guidance
- **1996 WHO** – Interchangeability guideline - cautious and vague attitude
- **1999 WHO** – "Blue book" – cautious recognition of BCS potential, no change in reserved position
- **2000 FDA** – Guidance on BA and BE waiver based on BCS, deals with INDs/NDAs, ANDAs and post-approval changes
- **2001 EU** – Note for guidance on BA and BE – takes BCS into consideration
- **2006 WHO** – Interchangeability guideline and specific BCS guideline proposing the implementation of BCS approach
- **2010 EU updated Guidelines adopted**
- **2012 FDA updated Guidelines adopted**
Biopharmaceutics Classification System

CLASS I
High solubility
High permeability

CLASS II
Low solubility
High permeability

CLASS III
High solubility
Low permeability

CLASS IV
Low solubility
Low permeability

Solubility
Permeability

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### Solubility Permeability BCS classification

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<th>Solubility</th>
<th>Permeability</th>
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<td>high</td>
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<td>I (e.g. Propranolol)</td>
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<tr>
<td>low</td>
<td>high</td>
<td>II (e.g. Glibenclamide)</td>
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<tr>
<td>high</td>
<td>low</td>
<td>III (e.g. Atenolol)</td>
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<tr>
<td>low</td>
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<td>IV (e.g. Azathioprine)</td>
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</table>
BCS BIOWAIVER is granted for

Rapid and similar dissolution.
High solubility & High permeability.
(BCS class 1)
Wide therapeutic window.
Basics of BCS

Dissolution of drug *in vivo*

determines

Drug Concentration

proportional

Intestinal Absorption
Pillars of the BCS

Solubility

Permeability
Absorption

Dissolution
**BCS Class Boundaries: Objectives**

- **Dissolution (Product)**
  - Rapid dissolution - ensure that in vivo dissolution is not likely to be the “rate determining” step

- **Solubility (Drug)**
  - High solubility - ensure that solubility is not likely to limit dissolution and, therefore, absorption

- **Permeability (Drug)**
  - High permeability - ensure that drug is completely absorbed during the limited transit time through the small intestine

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High solubility

- The highest single dose is completely soluble in 250 ml or less of aqueous solution at pH 1 - 6.8 (37 °C).

- Highest dose recommended by WHO (as recommended in the WHO Model List of Essential Medicines).
High permeability

♦ Revised EMA guidance: extent of absorption $\geq 85\%$ (absolute BA or mass balance data) or ‘known absorption’
♦ FDA guidance: absolute BA $>90\%$
♦ WHO guidance: extent of absorption at least 85\% in humans

• Human data are preferred; in-vitro data may be submitted if sufficiently justified and valid
Methods to investigate permeability

- PK-studies (e.g. absolute BA or mass-balance studies)
- Human intestinal perfusion studies
- Animal models
- *Caco 2 cell lines or other suitable, validated cell lines* (in-situ or in-vitro models for passively transported APIs only)
According to the WHO guideline drug substances that belong to

- **BCS-class 1 and 3**

- **and some of BCS class 2** (weak acids with high permeability)

... are in principle eligible for the BCS-based biowaiver approach
BCS-based biowaiver

*RISK assessment*

- “critical use medicines”
- “narrow therapeutic index drugs”
- “documented evidence for BA or BE problems”
- “scientific evidence that API polymorphs, excipients or the manufacturing process affects BE”
BCS-based biowaiver

Risk assessment on EXCIPIENTS acc. to WHO

Excipients – generally
- Should be ‘well-known’
- Used in ‘usual amounts’
- Without relevant impact on the absorption process

Preferred for class I drugs and requested for class III:
- same excipients in similar amounts as the reference

‘Critical’ excipients (e.g. surfactants, mannitol, sorbitol…)
should be qualitatively and quantitatively the same
BCS-based biowaiver

- BCS-based biowaiver are not just *in-vitro* dissolution,
- But *in-vitro* dissolution is meant to be an important part of BCS-based biowaiver applications
Minimize the risk by *thorough and correct* …

- drug substance classification
- In-vitro dissolution (incl. profile comparison)
- demonstration that excipients are
  - well-established
  - will not differ in terms of their effect on absorption
  - will not lead to interactions that alter pharmacokinetics
BCS - Implications for drug development

Application at early drug development and then in the management of product change through its life cycle

• Aids fundamental understanding of the biopharmaceutical and physical properties of the drug

• Aids discriminatory dissolution method development

• Can help guide the development of in-vitro/in-vivo correlations

• Can be used to obtain a biowaiver

• Development of poorly soluble drugs
Applications of BCS in oral drug delivery technology

Class I - High Permeability, High Solubility

- Achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile.
- Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug.
Different approaches are adopted:

• Micronisation,
• Addition of surfactants,
• Formulation as emulsions and microemulsions systems,
• Use of complexing agents like cyclodextrins to enhance solubility
Require the technologies that address to fundamental limitations of absolute or regional permeability.

Peptides and proteins constitute the part of class III and the technologies handling such materials are on rise nowadays.
Class IV - Low Permeability, Low Solubility

Major challenge for development of drug delivery system, and the route of choice for administering such drugs is parenteral (solubility enhancers.)

Fortunately, extreme examples are the exception rather than the rule and are rarely developed, and rarely reach the market.
Limitations of BCS as a Predictor of Drug Disposition

- Permeability (90% absorption) is difficult to determine, and difficult to convince the regulatory agencies.

- There is little predictability for BCS classification drugs beyond Class 1 primarily due to the difficulty of determining and proving 90% absorption.
  - many drugs can be misclassified
Conclusion

- BCS aims to provide a regulatory tool for replacing certain BE studies by accurate in-vitro dissolution tests.
- This increased awareness of a proper biopharmaceutical characterization of new drugs may in the future result in drug molecules with a sufficiently high permeability, solubility and dissolution rate, and that will automatically increase the importance of the BCS as a regulatory tool over time.
Thank you...
Any questions...