Brand vs Generic- Regulatory Perspective

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Role of Regulatory Affairs

- Group or department that is responsible for registering product with the Health Authority
  - Prepare regulatory submission strategy
  - Prepare dossier as per market requirements
  - Submit to the respective heath authority
  - Answer queries and secure approval
  - Maintain the license and registration per legal regulatory framework

Brand vs Generic- Outline

- **Criteria for a Generic Drug**
- **How it differs from the innovator or brand dug**
  - Developmental phases
  - Regulatory submission Pathway
  - High Level Data requirements
  - Dossier structure

What is an Innovator Drug?

- An **innovator drug** is the first **drug** created containing its specific active ingredient to receive approval for use.
- It is usually the product for which efficacy, safety and quality have been fully established.
- When a new **drug** is first made, **drug** patent usually will be acquired by the founding company.
- Sold in a Market under a catchy **Brand Name**
- Gets the status as Reference Listed Drug or RLD by MOH

What is a Generic Drug?

- **Generic drugs** have the same active ingredients as **brand name drugs** already approved by the MOH.
- Generics only become available after the patent expires on a **brand name drug**.
- A generic drug is a medication created to be the same as an already marketed brand-name drug in active ingredient, strength, dosage form, route of administration, intended use, quality, and effectiveness
- These similarities help to demonstrate bioequivalence, which means that **a generic medicine works in the same way and provides the same clinical benefit as its brand-name version.**
- In other words, you can take a generic medicine as an equal substitute for its brand-name counterpart[1], typically designated as a Reference Listed Drug

1) Generic Drugs: Questions and Answers: https://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm

Generic Drug must compare with Reference Listed Drug

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Same Label, except indications in the innovator label protected by patents and exclusivity, can be left out by Generic

Reference Listed Drug FDA Database

- Every MOH maintains such database and its critical to know what is the RLD in a particular market before
- By designating a single RLD as the standard to which all generic versions must be shown to be bioequivalent, the MOH intends to avoid possible significant variations among generic drugs and brand counterparts
- Reference Listed Drugs are designated in a data base called Orange Book
- RLD is an FDA-approved drug product to which new generic versions are compared to show that they are bioequivalent.
- A drug company seeking approval to market a generic equivalent must refer to the RLD in its generic application.

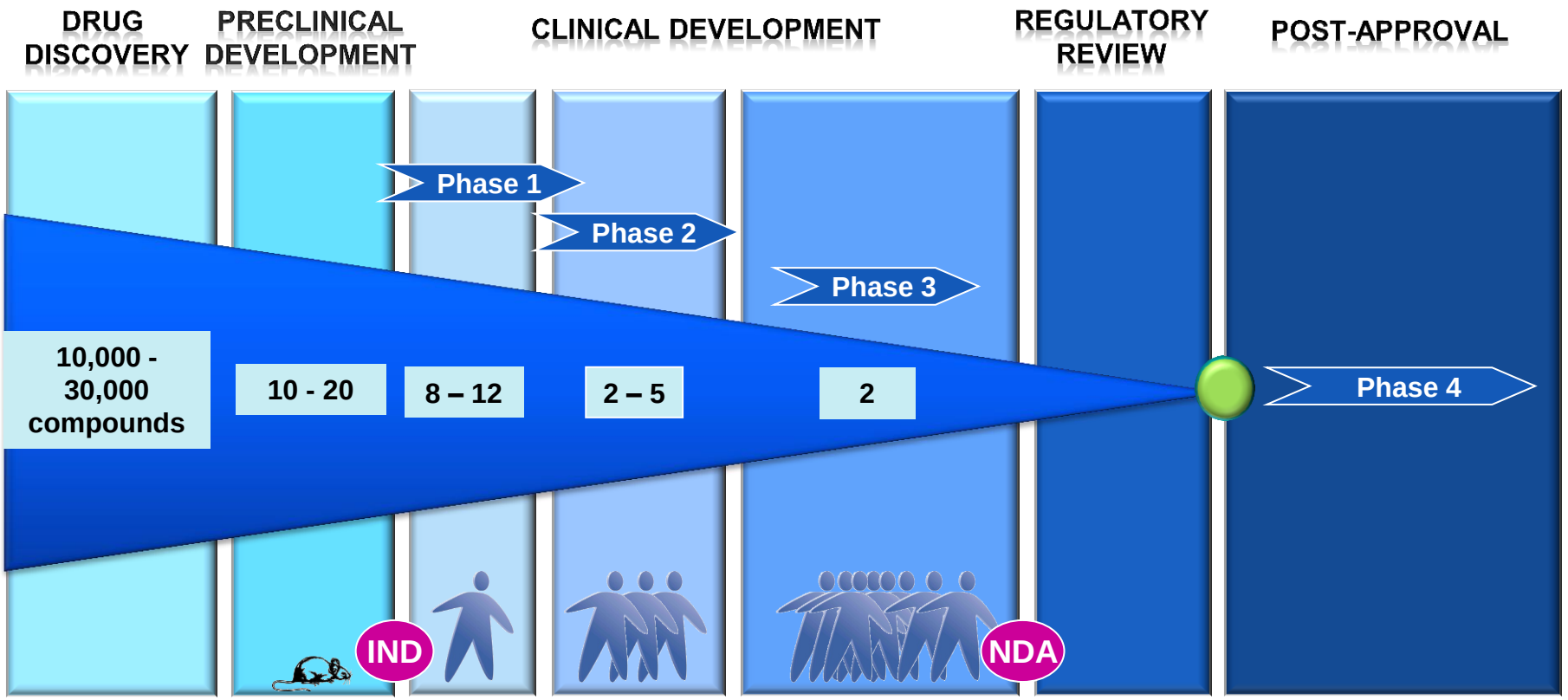
Where a Generic Drug can differ from RLD?

- **A generic drug may differ from the RLD or Innovator:**
  - Certain excipients (antioxidants, preservatives, buffers) may be different as long as replacement is safe and does not affect performance of the product
  - Sometimes replacements improve performance of a Drug and Generic version may be better than RLD
  - Drug substance or drug product-related impurities
    - Process impurities
    - Residual Solvents
    - Leachable and Extractables
    - Elemental Impurities

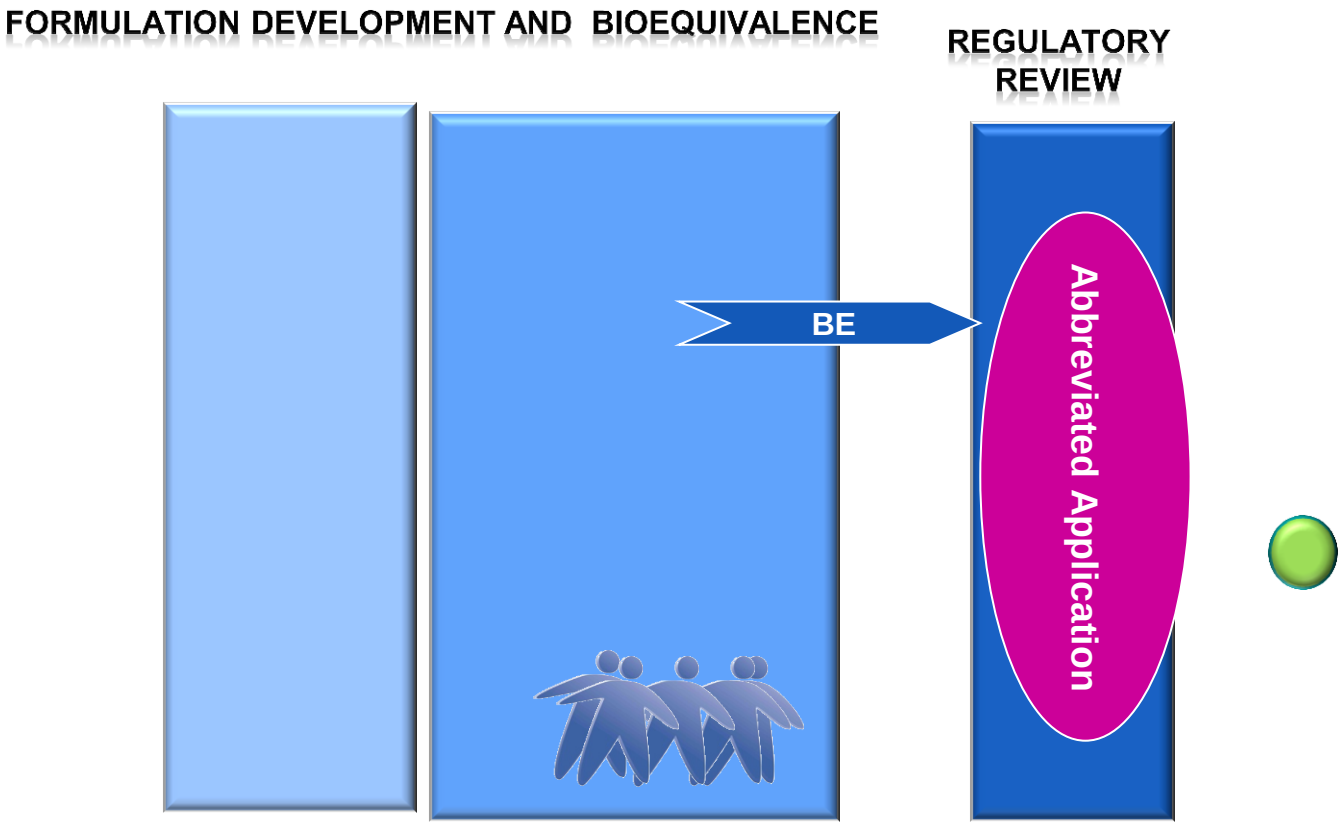
Regulatory Submission highlights

- A generic drug is allowed to be registered via an abbreviated dossier
- A new-molecular entity (NME) before becoming innovative drug undergoes extensive testing to establish the safety and efficacy of finished formulation
- A generic equivalent relies on the safety and efficacy established by the RLD/innovator product and need not repeat it
- The aim for Generic is to establish bioequivalence with RLD

Innovative Drug Development Process



Simple Generic Drug Development Process



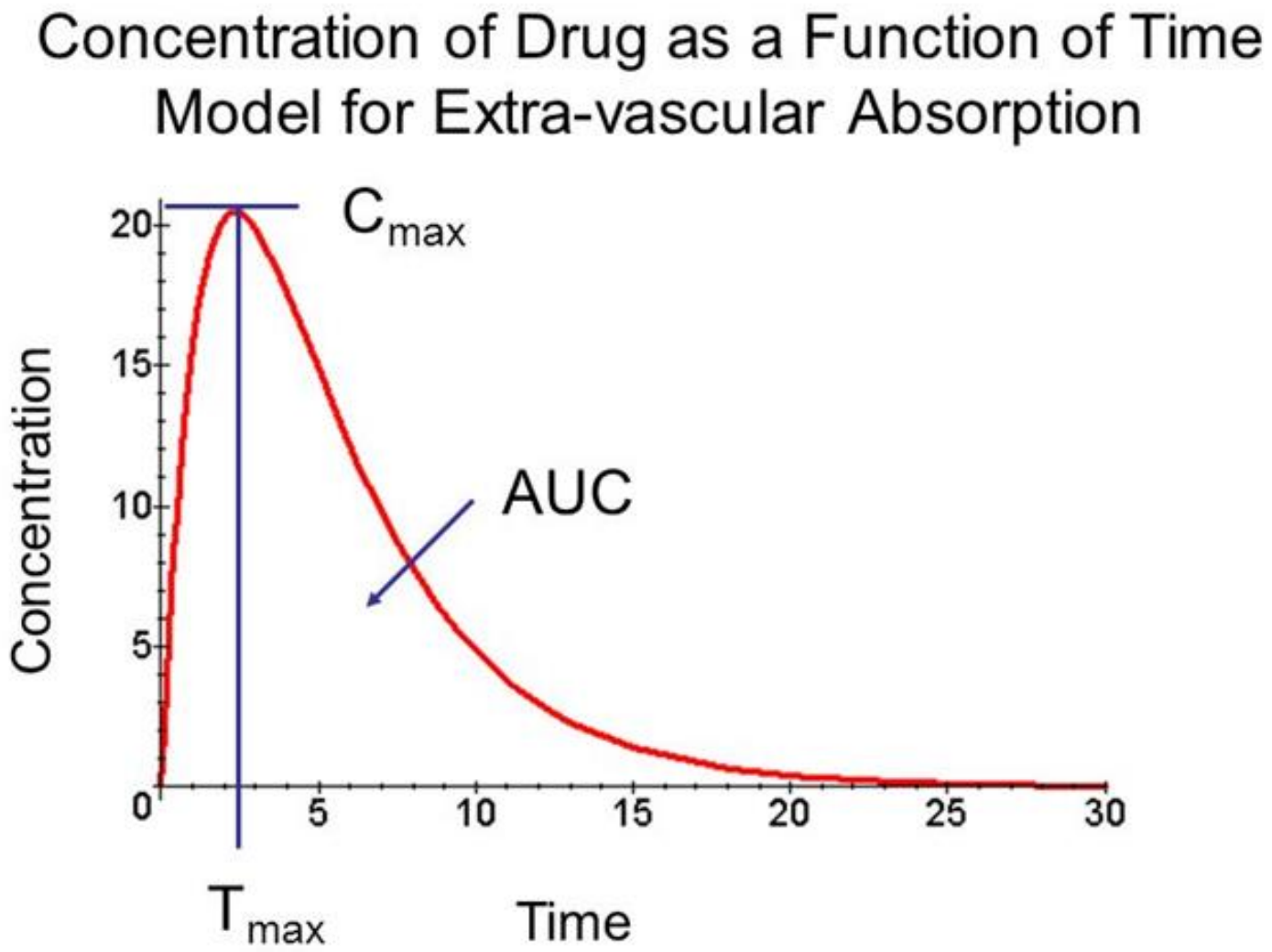
What is Bioequivalence?

- An important criteria that a Generic drug must meet
- By FDA- “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 becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study”
- By EMA-Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bio-availabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

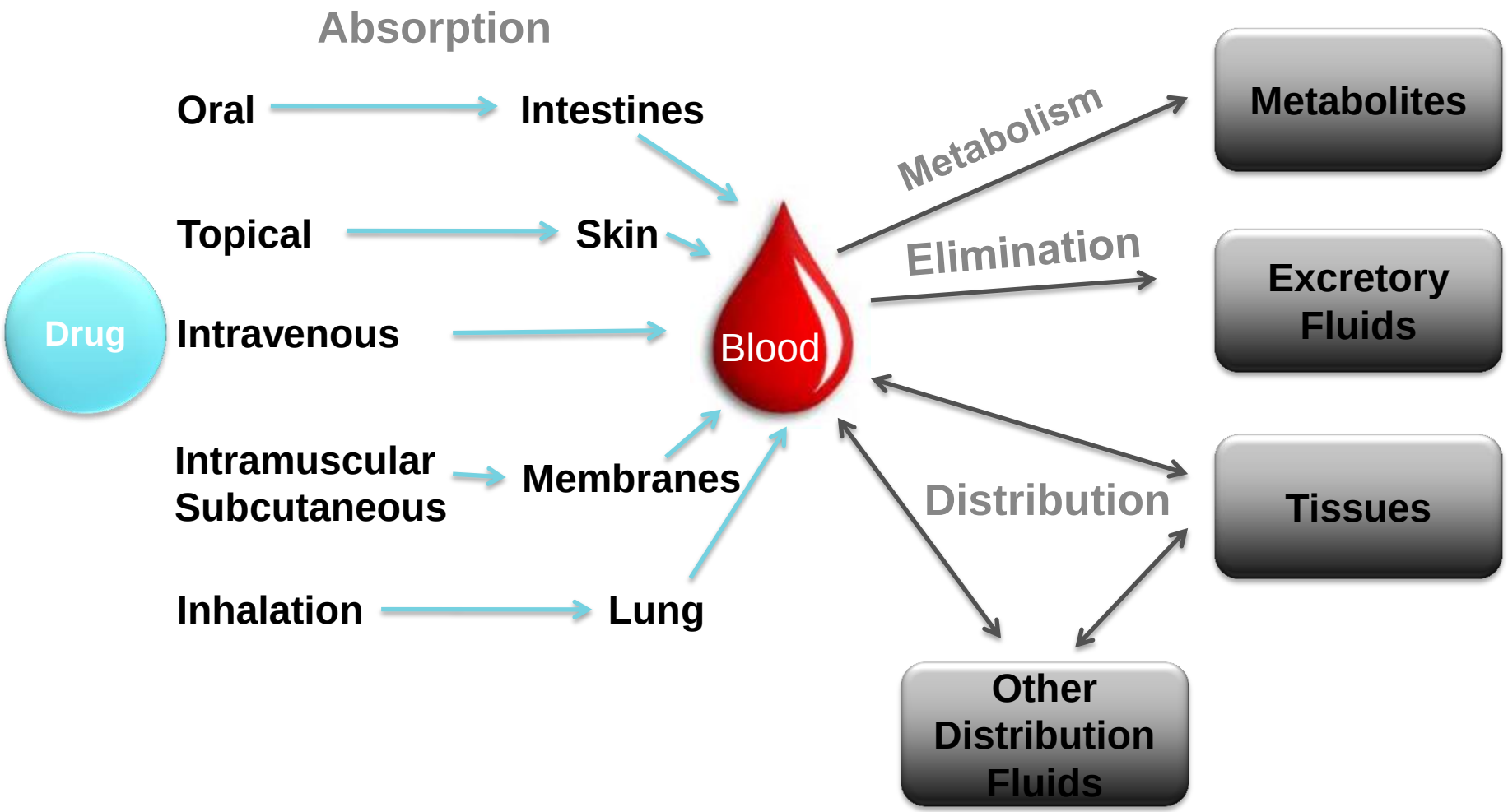
What is Bioavailability?

- Amount of a substance that becomes available (reaches the target organ or systemic circulation) to an organism's body for bioactivity when introduced through ingestion, inhalation, injection, or skin contact.
- Measured mathematically as the rate (Cmax, Tmax) and extent (Cmax and AUC) to which the active ingredient becomes available at the site of action

Bioavailability Assessment



Dosage Forms and Bioavailability



C. Gunarathna, Drug Metabolism & Pharmacokinetics in Drug Discovery, *Current Separations* 19:1 (2000)

BIO-WAIVER

Exemption from conducting human clinical trials

- Major MOHs have bio-waiver guidance
- Some formulations (simple Injectables) are automatically exempted
- Other formulations can be justified using in-vitro test for ex. Oral tablets using comparative Dissolution data
- In case of multiple strengths, highest strength is subjected to BE study and other proportional strengths qualify for bio-waiver
- A strong justification based on scientific data is required to support Biowaiver request for complex Injectables
- A formal BW request and discussion with MOH happens prior to the submission

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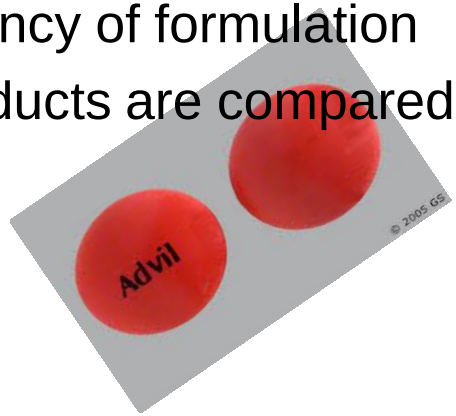
Comparative Dissolution for Bio-waiver in Oral solid dosages

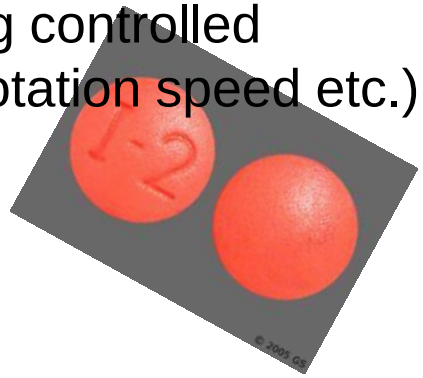
- Dissolution data is a very good indicator of efficiency of formulation
- Dissolution profiles of Generic and Innovator products are compared in vitro under identical conditions
- It measures the % of the API that

  (1) has been released from tablets/capsules/ suspensions/suppositories and

  (2) has dissolved in the dissolution medium during controlled testing conditions (apparatus, medium, volume, rotation speed etc.) within a defined period

  – The tablet thus first disintegrates
  – Then the API will be able to dissolve
  – Slow disintegration ➜ slow dissolution
  – The % API dissolved is determined with an appropriate validated method: UV/VIS, HPLC, AA, GC, etc.





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Apparatus (choice)	Paddle, 50 (75) rpm or Basket, 100 rpm
Dissolution media All three media for full comparison	Buffer pH 6.8 or simulated intestinal fluid without enzymes Buffer pH 4.5 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, (60, 120) min. (typical)
Units (individual)	12 for “official” studies

Two conditions to determine if the dissolution profiles of two products/batches in <u>a particular dissolution medium</u> are similar:

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

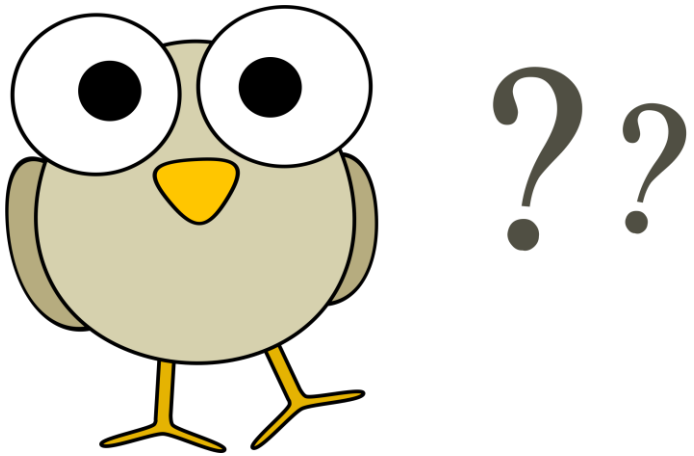
   If not:
2. Calculate the f_2 value (similarity factor):
   - If $f_2 \geq 50$, the profiles are normally regarded similar

When are dissolution properties of two products regarded similar?

The profiles should be similar in all three media

- Statements of instability or insolubility are not acceptable, but should be demonstrated / justified

Questions???



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Knowledge check

Circle one : True or False

1. **A Generic Drug must be a carbon copy of Innovator Drug?**

T F

2. Only Intravenous Route of Administration is 100% bioavailable

T F

3. All oral solid dosages are subjected to bio-equivalence clinical trials in humans

T F

Knowledge check

Agencies may allow replacement of antioxidant found in RLD in a Generic formulation if

- It is cheap
- It is safe
- It is determined safe and will not alter performance of the drug
- All of the above

Knowledge Check

Which of the following is the correct definition of bioavailability?

- Bioavailability describes the proportion of the drug administered that is metabolised very quickly and thus is not available to induce a physiological effect.
- Bioavailability describes the ability of the administered drug metabolites to cause undesirable physiological effects.
- Bioavailability is used to describe the fraction of the dose of drug administered that is present within the body and facilitates the desired physiological effects.
- Bioavailability is the length of time an administered drug is present in the body and thus is available to cause a physiological effect.

Measuring bioavailability of a substance:

- Allows the MOH to determine if a proposed generic formulation is bioequivalent to a name brand drug
- Allows the MOH to determine if a vitamin supplement will do what the manufacturer claims
- Allows the MOH to measure how quickly you will get well
- Allows the MOH to determine whether you will have side-effects from a particular drug formulation