A Primer on Generic Drugs and Bioequivalence: an overview of the generic drug approval process

Division of Bioequivalence II
Reviewer
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What is a Generic Drug?

A copy of a brand-name drug, which must have the:

same quality
same safety
same strength

Both brand name and generic drugs:

are approved by the FDA
must meet the same FDA standards for quality

Generic equivalents for a brand name drug are listed in the “Electronic Orange Book”

Myths about Generic Drugs

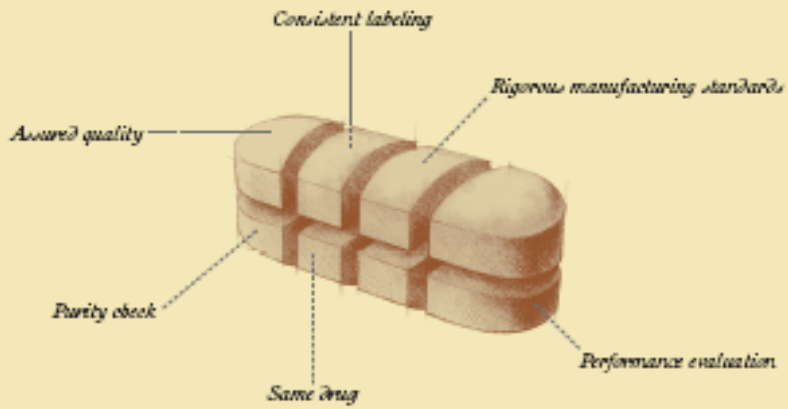
- **Generics…are not as safe**
- **Generics…are not as potent**
- **Generics…take longer to act in the body**
- **Generics…are made in sub-standard manufacturing facilities**

Think it's easy becoming a

generic drug

in America?

Think again.



FDA ensures that your generic drug is safe and effective. All generic drugs are put through a rigorous, multi-step approval process. From quality and performance to manufacturing and labeling, everything must meet FDA's high standards. We make it tough to become a generic drug in America so it's easy for you to feel confident. Visit www.fda.gov/cder/ or call 1-888-INFO-FDA to learn more.

Generic Drugs: Safe. Effective. FDA Approved.

FDA U.S. Food and Drug Administration

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FDA Legislative Support for Generic Drugs

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, made ANDAs possible by creating a compromise in the drug industry. Generic drug companies gained greater access to the market for prescription drugs, and brand-name companies gained restoration of patent life of their products lost during the FDA's approval process.

Generic Competition

It is essential to have brand-name and generic drugs available

to meet the patient demand

to keep insurance premiums down

to save consumers $10+ billion yearly

generics represent 65% of the total prescriptions dispensed in the US

Patent Protection

A patent:

Protects the investment of the drug company that developed the brand-name drug

Gives the drug company the sole right to sell the drug while the patent is in effect

Patent Protection

When the patent on a brand-name drug nears expiration, drug companies that want to manufacture a generic can apply to the FDA to sell a generic version of the drug.

Generic Review

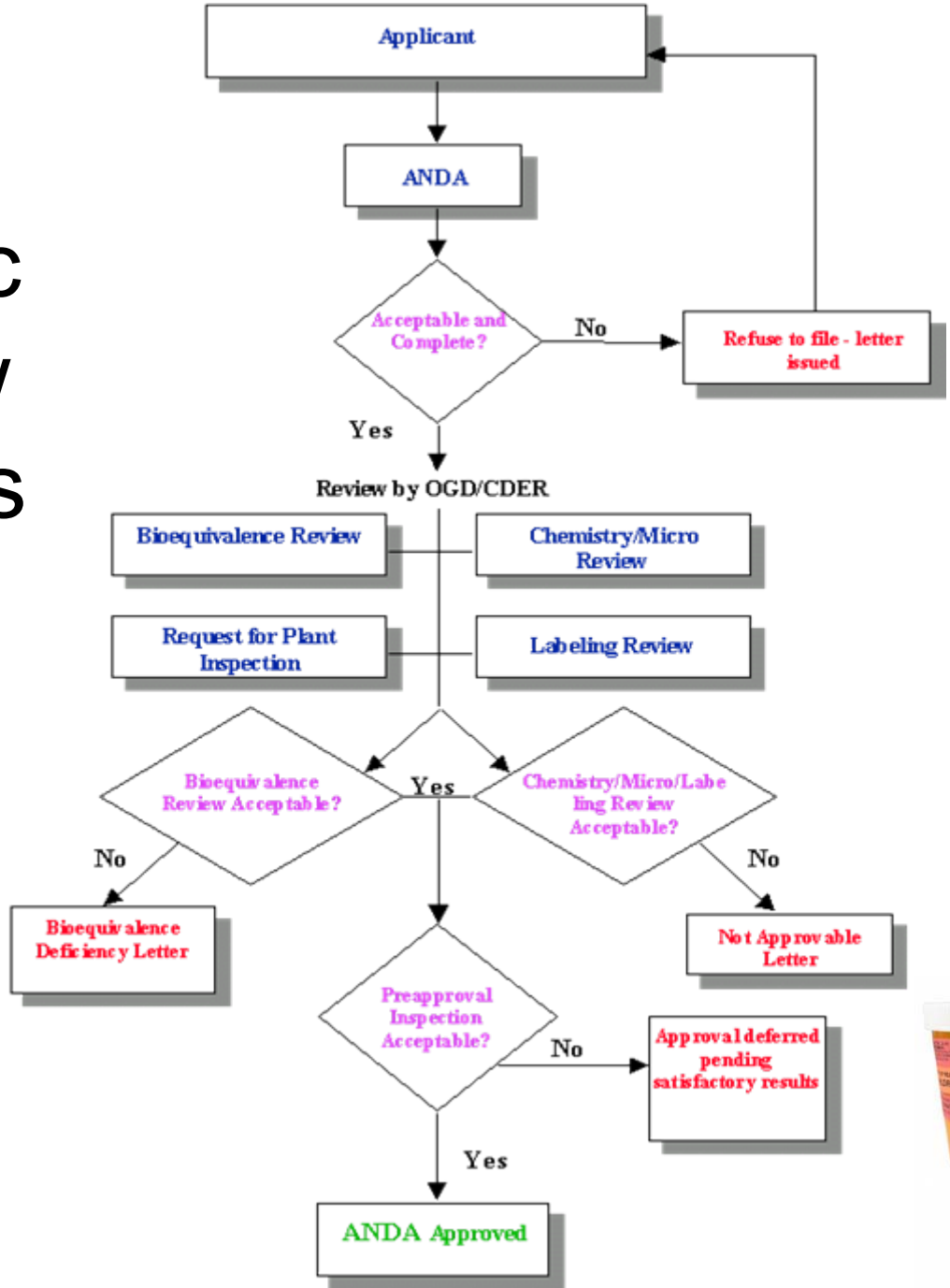
- Brand Name Drug (NDA) Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

- Generic Drug (ANDA) Requirements

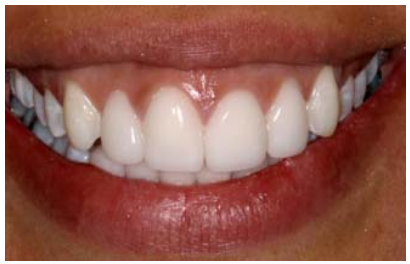
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

Generic Review Process

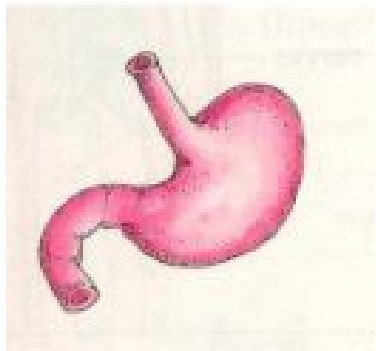


The Bioequivalence Review Process

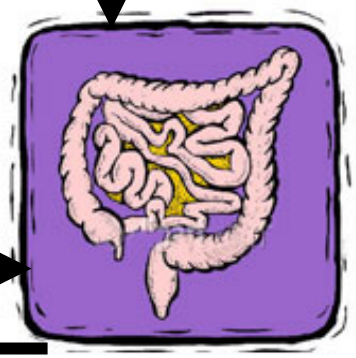
Path of Drug: From Tablet to Blood

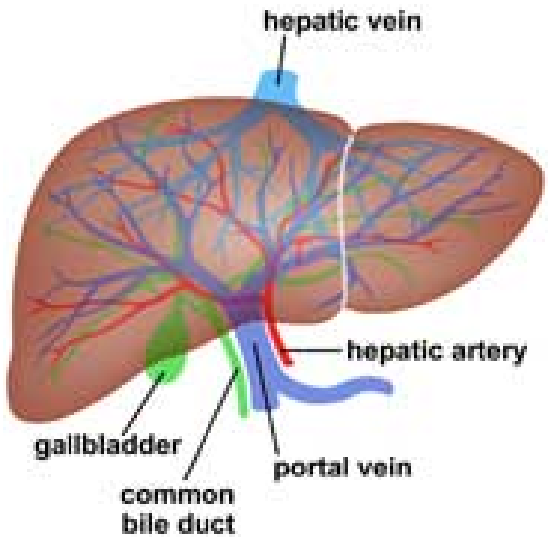


Acidic pH

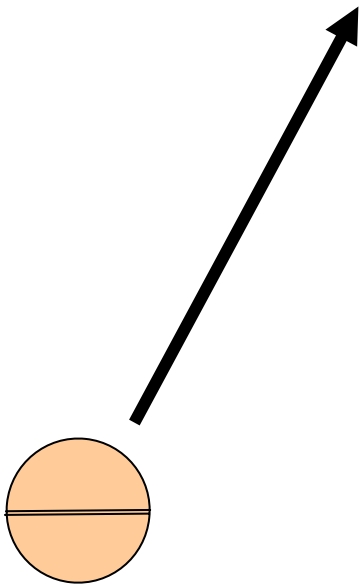


Basic pH

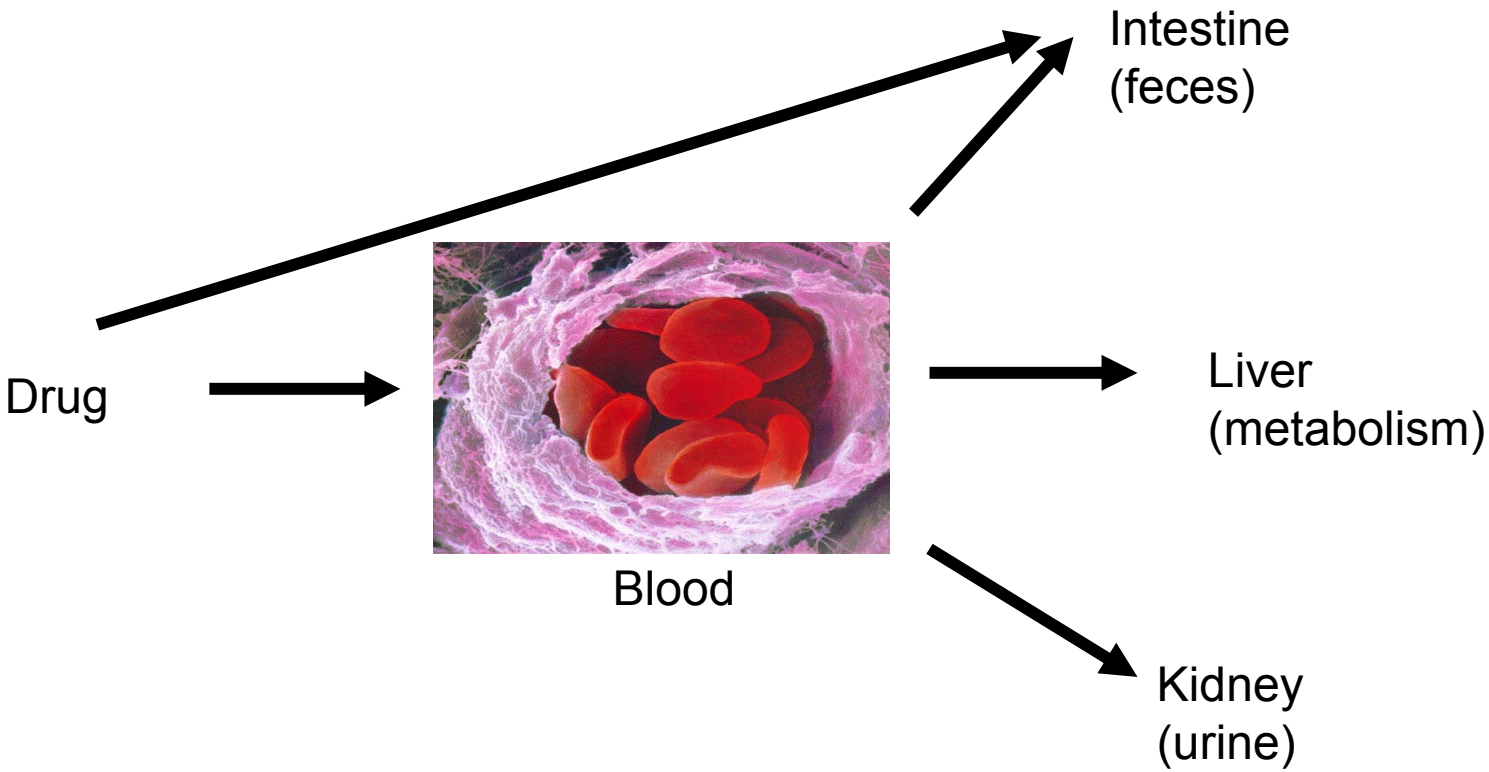




Metabolism?



Pathways of Drug Elimination



Definition of Bioequivalence

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.

Definition from 21 CFR § 320.1

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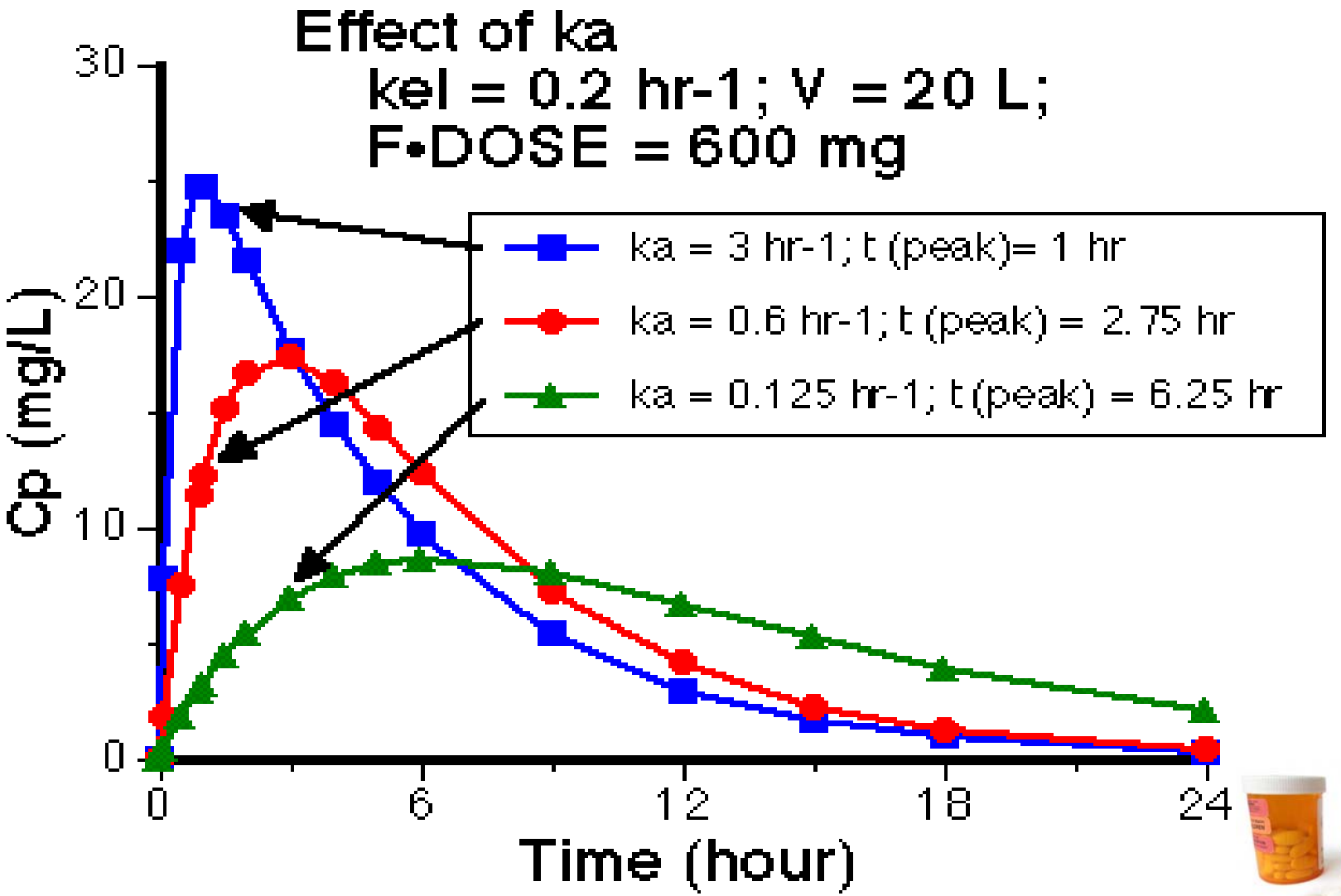
Rate is Essentially Measured by Cmax

- **Cmax is the maximum observed concentration**
- **Cmax tends to have higher variability**
- **Need adequate sampling time-points**

Cmax with Varying Absorption Rates



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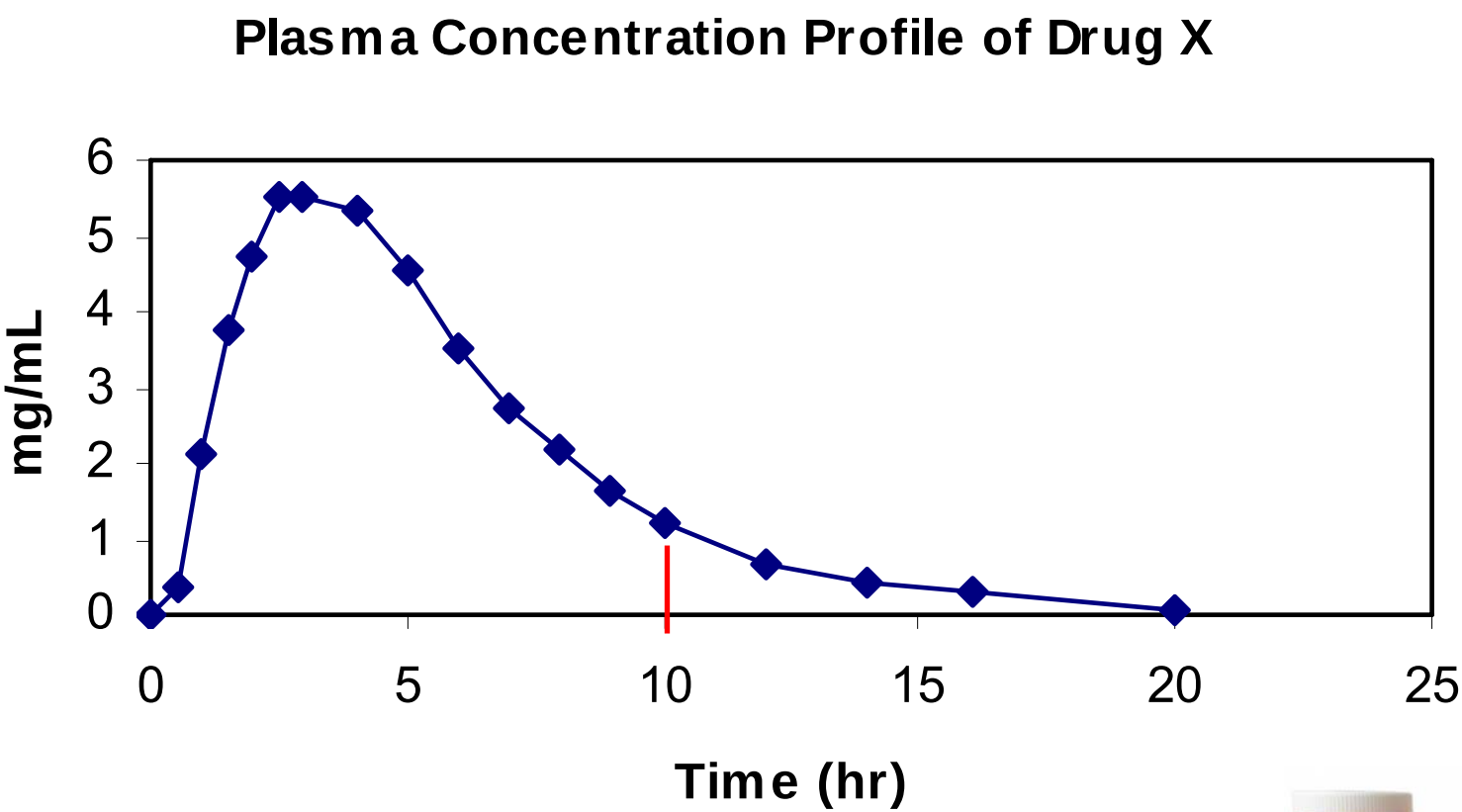
Extent of Absorption is measured by Area Under Curve (AUC)

- **AUCt is a measure of the total exposure of drug to the body up to the last sampling time**

- **AUCinf is a theoretical measure of the total exposure of drug to the body from administration till all the drug is eliminated**

Extent of absorption is Measured by Area Under Curve (AUC)



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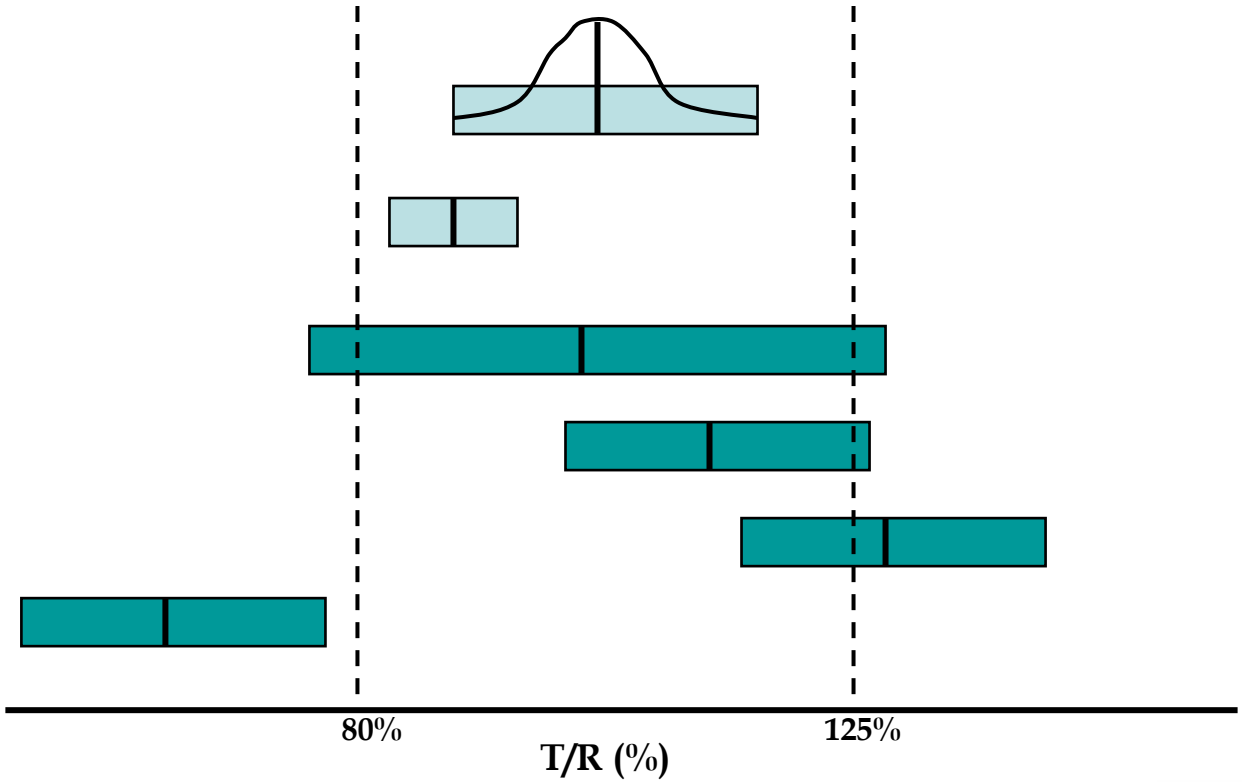
Possible BE Results (90% CI)



Example of Data Output

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
	6926.21	7073.05	0.98	88.52-108.32
	7272.94	7442.56	0.98	88.79-107.55
	1014.78	1067.66	0.95	87.18-103.62

General Methods for Establishing BE of Solid Oral Dosage Forms

In Vivo

- **Pharmacokinetic**
  - Cmax, AUCt, and AUCinf
- **Pharmacodynamic**
  - Useful when drug levels can not be measured or are not relevant

In Vitro

- **Dissolution**
  - Non Bio-problem drugs, non-bio strengths
- **BCS**
  - Highly permeable, Highly Soluble Drugs

How is a Pharmacokinetic (PK) BE Study Conducted?

- **Study Design**
  - Need a study design to allow us to assess absorption and differentiate between formulations

2-way Single Dose Crossover Design

- Two treatments:
  - single dose of test product (**A**)
  - single dose of RLD (**B**)
  - two periods
  - two sequences: **AB** and **BA**

- The subjects are randomly assigned to the sequences

2-way Single Dose Crossover Design

Sequence I

A → **Period I** — **Washout Period** — **B** → **Period II**

Sequence II

B → **Period I** — **Washout Period** — **A** → **Period II**

A=Test Drug **B**=RLD

Other Designs

- **Parallel Design**

Treatment 1 ⟶ **A**

Treatment 2 ⟶ **B**

- **Replicate Design**
  - 4 period (ABAB and BABA)

Types of *in vivo* BE Studies

- **Fasting Study**
- **Non-fasting (a.k.a. Fed) Study**
- **Sprinkled-fasting (or fed) Study**

Components of in vivo BE Study

- **Clinical**
- **Bioanalytical**
- **Statistical**

Clinical Study Considerations

- Normal healthy subjects
  - Exception: patients
  - Male and Female
  - Racially diverse
- Strength of the test drug chosen
- Sampling time
- Protocol deviations
- Adverse event monitoring
- If fed study: high fat, high calorie breakfast

Statistical Considerations

- Subjects were included/excluded based on SOP for statistical analysis
  - Emesis
  - First non-zero concentration > 5% of its Cmax
  - Pre-dose concentration
  - Parent vs. metabolite

- 90% Confidence Interval (CI) acceptance criteria is 80.00-125.00% for the test/reference ratio for all three parameters AUC_t, AUC_{inf}, and C_{max}

Dissolution Testing

- **Definition of dissolution**

  noun: the process of going into solution; "the dissolving of salt in water" [synonym: dissolving]

- **Importance of dissolution**
  - Bioavailability information
  - Batch to batch consistency
  - In vitro process

Dissolution Testing (contd.)

- **Use of dissolution in Generic drugs**
  - In vitro characterization
  - Bio-waiver
  - BCS drugs

- **About dissolution testing**
  - Apparatus
  - Media
  - Volume
  - Speed
  - Time

Dissolution Testing (contd.)

- **Dissolution profile comparison**
  - Test vs. test; RLD vs. RLD
  - Different type of release products
  - Dose dumping (in different pH and alcohol)
  - f2 similarity factor calculation: f2≥ 50 is considered similar

- **Setting of dissolution specifications**
  - Immediate release products
  - Delayed release products

Dissolution Methods: Search Results - Microsoft Internet Explorer

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Address http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

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Dissolution Methods for Drug Products

Search Results for 'abacavir'

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Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Abacavir	Tablet	II (paddle)	75	0.1 N HCl	900	5, 10, 15, and 30 min	03/22/2006

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Dissolution Methods Disclaimer

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FDA/Center for Drug Evaluation and Research
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Division of Bioequivalence
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Local intranet

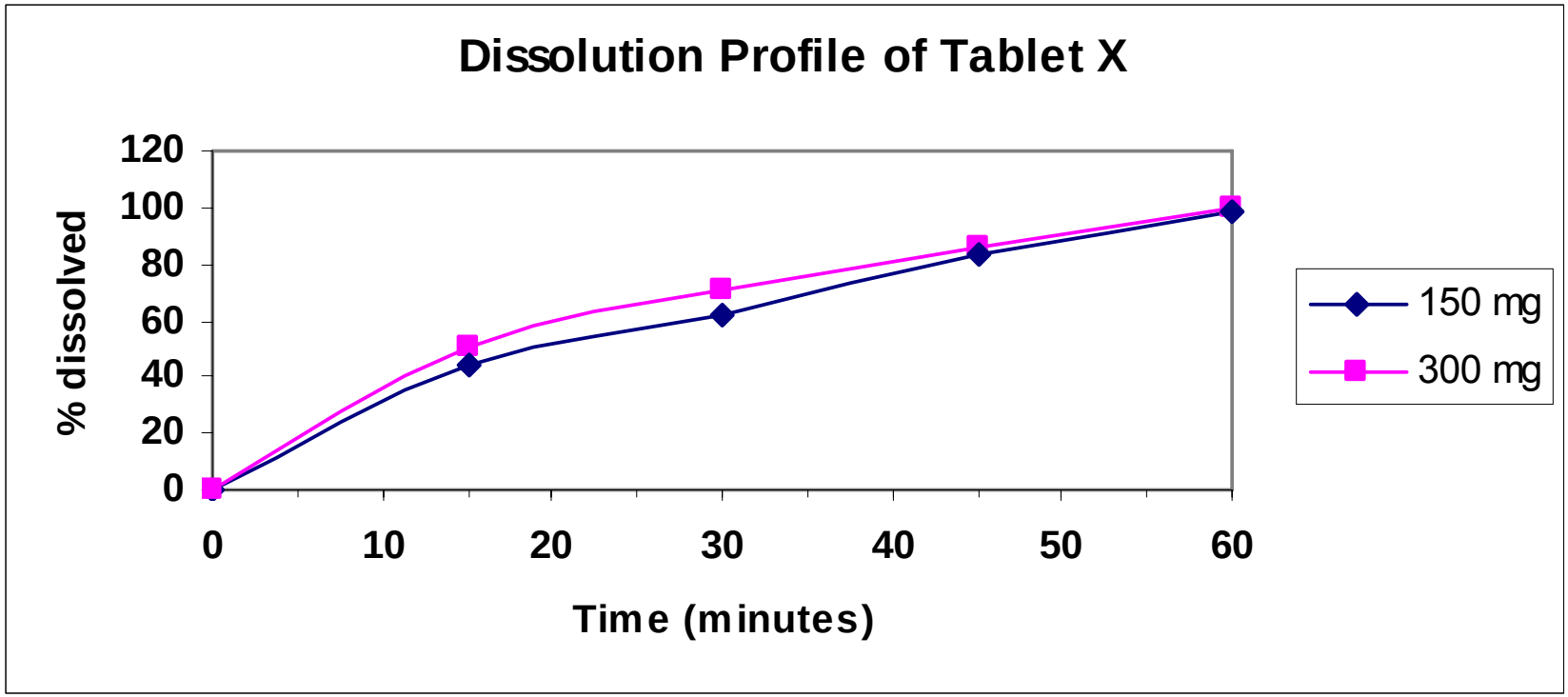
Bio-waivers

- The cost of conducting a bioequivalence study is quite expensive
- Some drug products have several strengths
- Waivers are granted for the non-bio strengths

Formulation Data

Components	150 mg (mg/tab)	300 mg (mg/tab)
Core Components		
Active, USP	166.65 (71.21%)	333.3 (71.21%)
Ethyl Cellulose, NF	15.8 (6.75%)	31.6 (6.75%)
Alginic Acid, NF	20.0 (8.55%)	40.0 (8.55%)
Corn Starch, NF	8.75 (3.74%)	17.5 (3.74%)
Microcrystalline Cellulose, NF (Avicel PH-102)	12.5 (5.34%)	25.0 (5.34%)
Sodium Lauryl Sulfate, NF	0.75 (0.32%)	1.50 (0.32%)
Magnesium Stearate, NF	2.55 (1.09%)	5.10 (1.09%)
Tablet Core Weight	**227.0**	**454.0**
Film Coating Components		
Opadry II Pink	6.82 (2.91%)	N/A
Opadry II Red	N/A	13.61 (2.91%)
Opadry Clear	0.21 (0.09%)	0.41 (0.09%)
Purified Water USP	--	--
Film coated tablet weight	**234.03**	**468.02**

Dissolution Profile



f2 = 62.3

Additional Information

- www.fda.gov/cder/ogd
- http://www.fda.gov/cder/ob/default.htm

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Questions