

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

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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”**

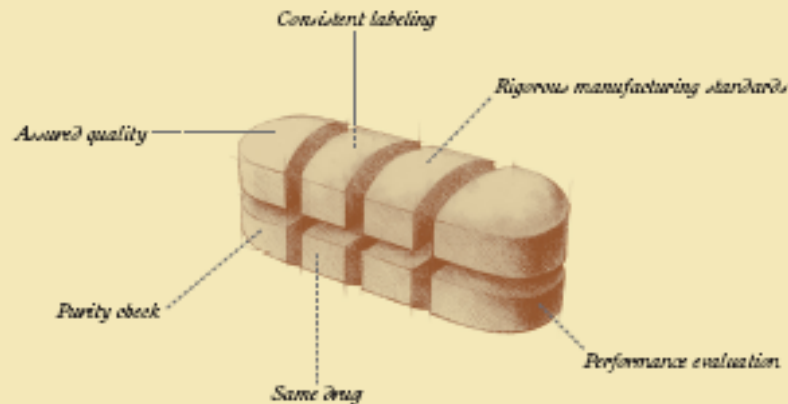


# Myths about Generic Drugs

- **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/](http://www.fda.gov/cder/) or call 1-888-INFO-FDA to learn more.

**Generic Drugs: Safe. Effective. FDA Approved.**



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

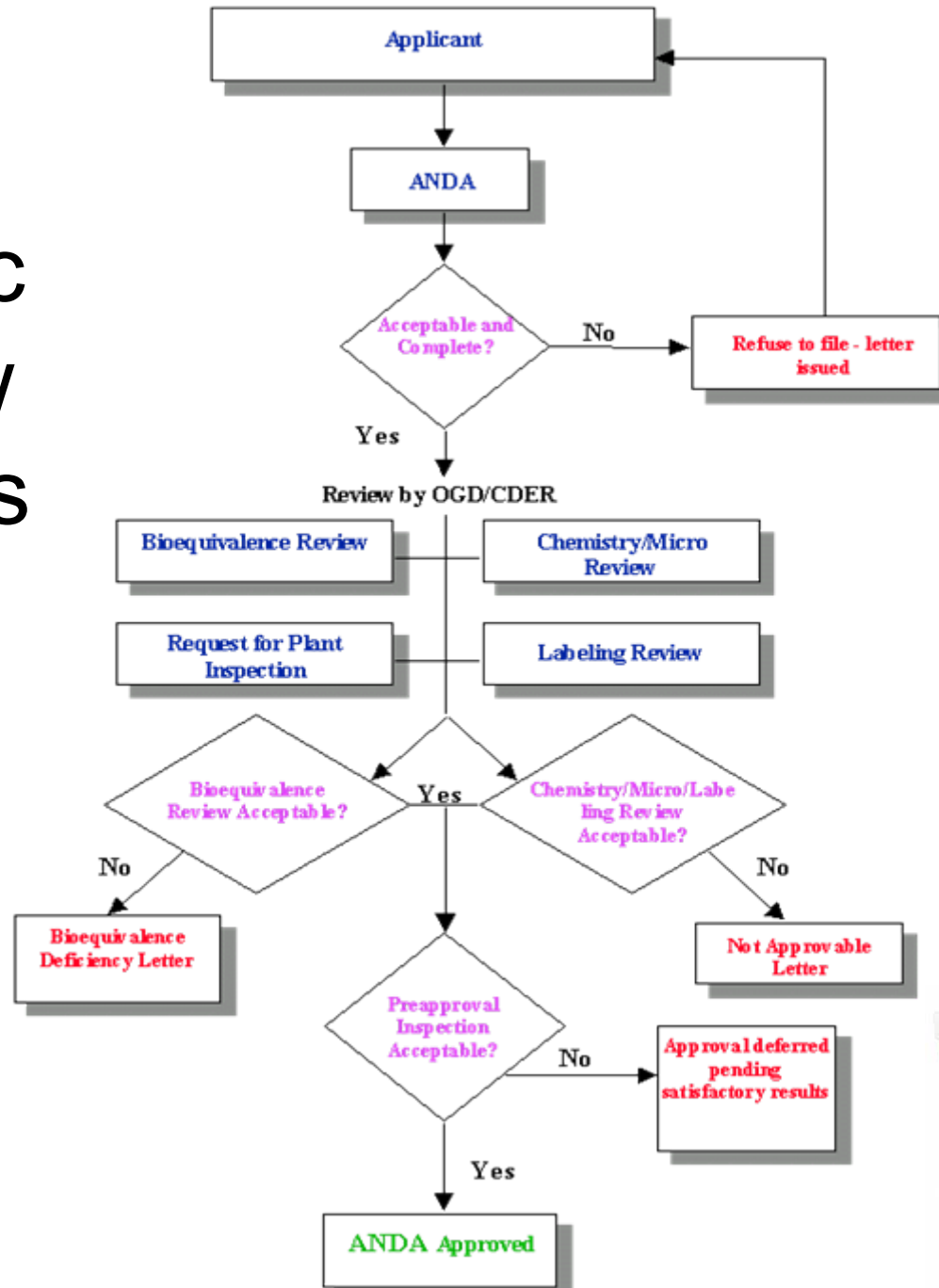
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

- Generic Drug (ANDA) Requirements

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



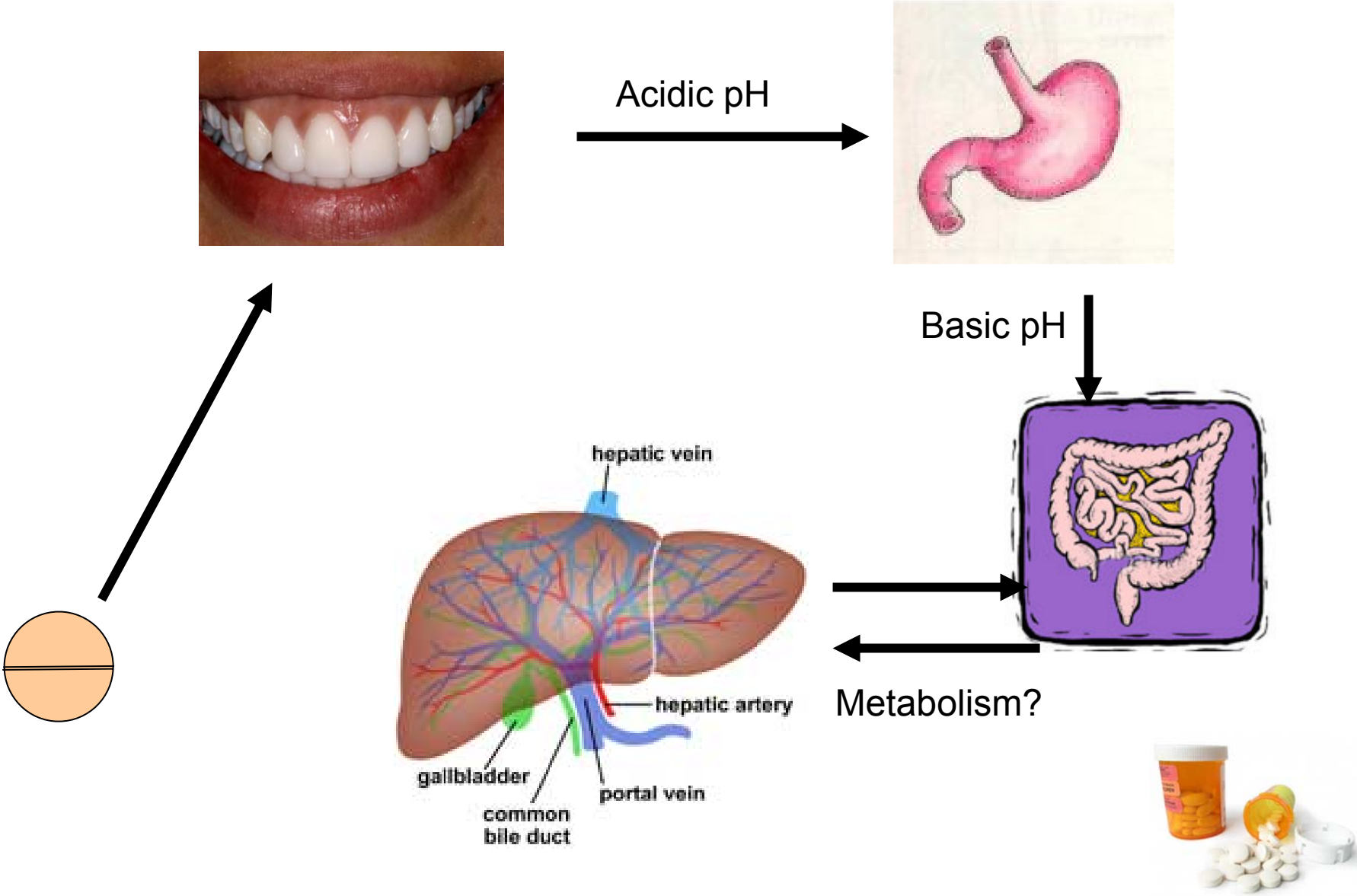
# Generic Review Process



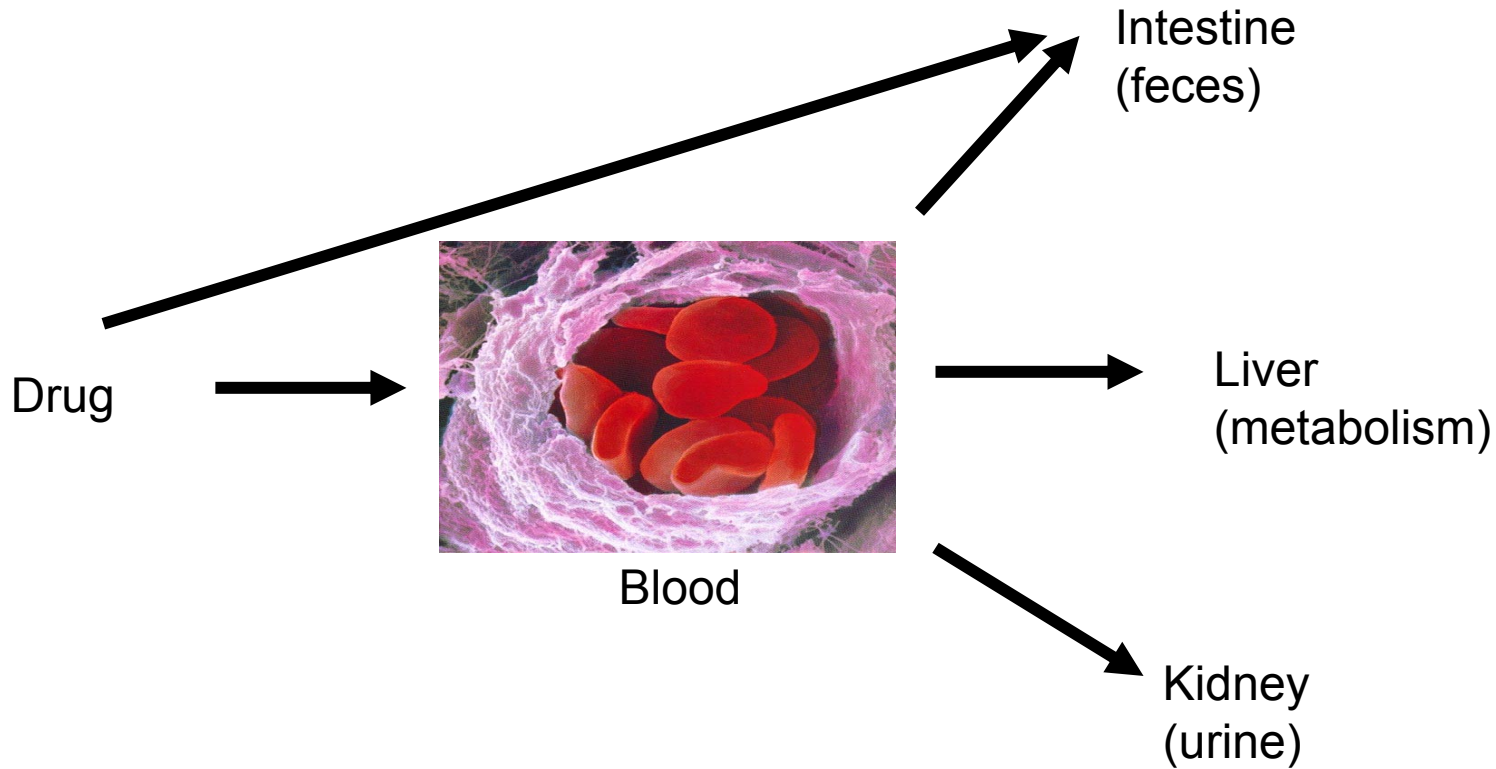
# The Bioequivalence Review Process



# Path of Drug: From Tablet to Blood



# 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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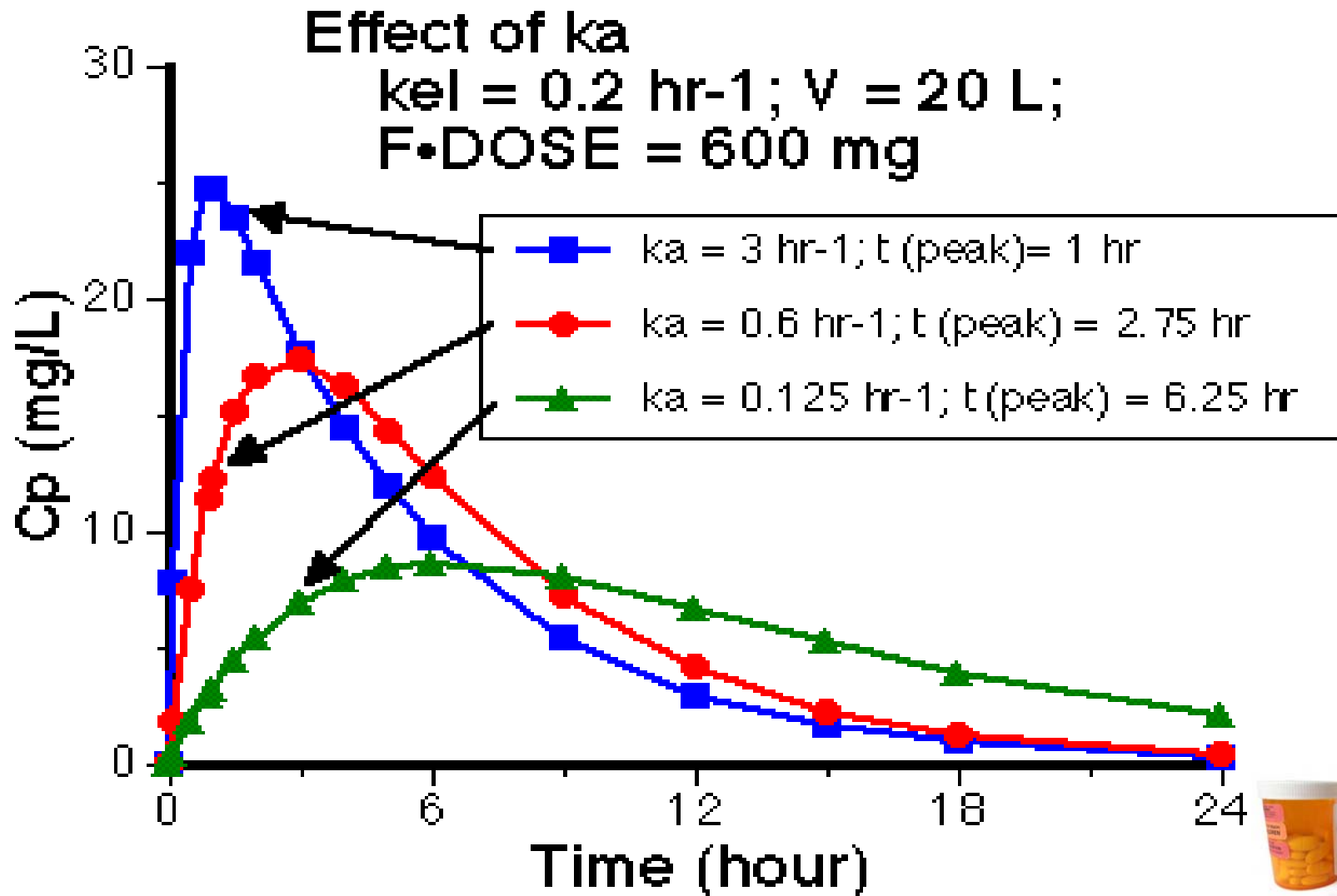


# Rate is Essentially Measured by $C_{max}$

- **$C_{max}$  is the maximum observed concentration**
- **$C_{max}$  tends to have higher variability**
- **Need adequate sampling time-points**



# Cmax with Varying Absorption Rates



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



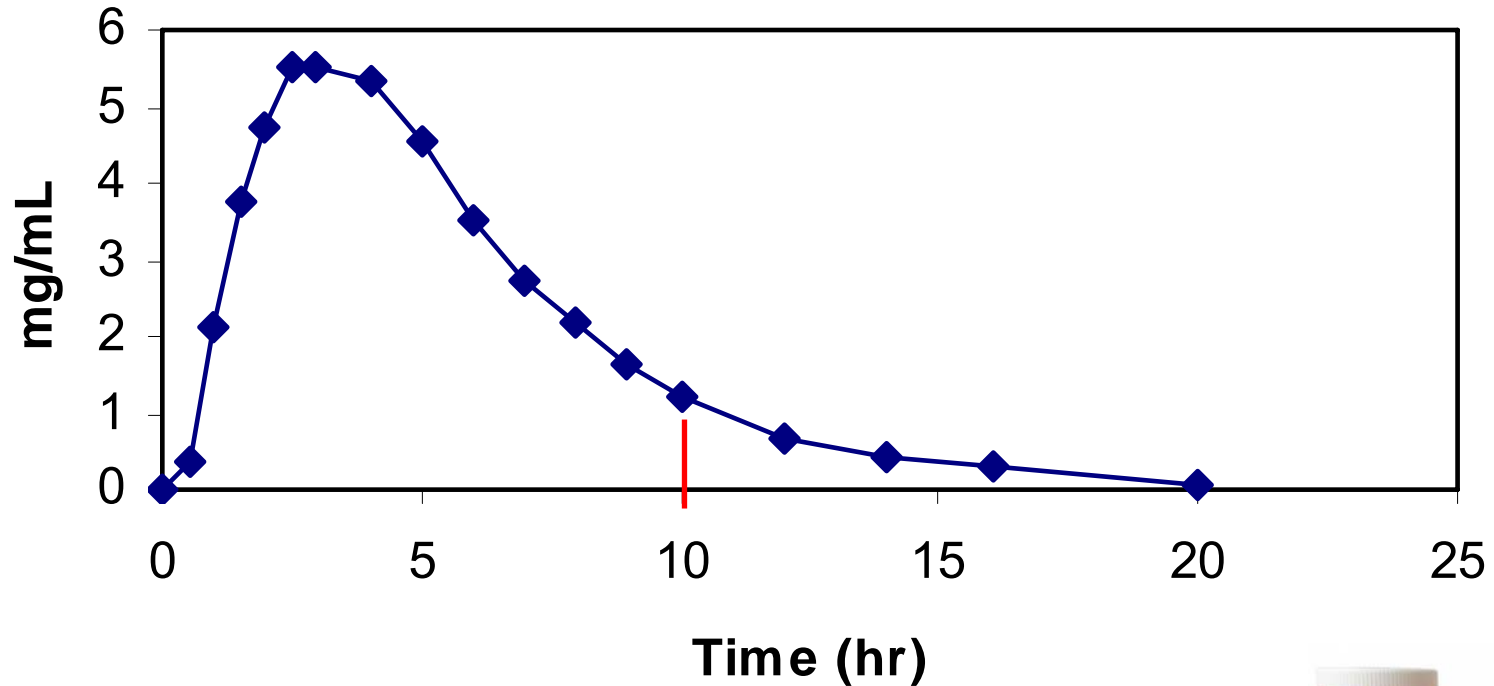
# Extent of Absorption is measured by Area Under Curve (AUC)

- **AUC<sub>t</sub> is a measure of the total exposure of drug to the body up to the last sampling time**
- **AUC<sub>inf</sub> 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)

## Plasma Concentration Profile of Drug X

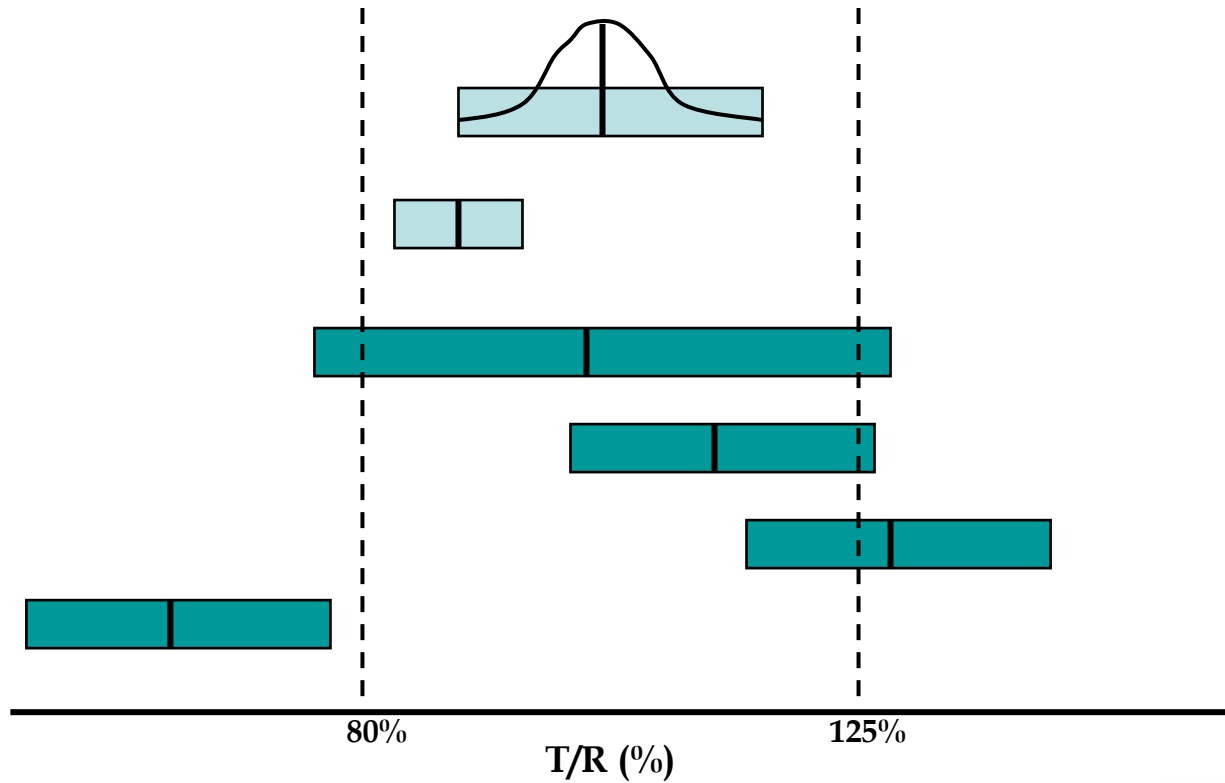


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# Possible BE Results (90% CI)



# 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**
  - C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>inf</sub>
- **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



## Sequence II



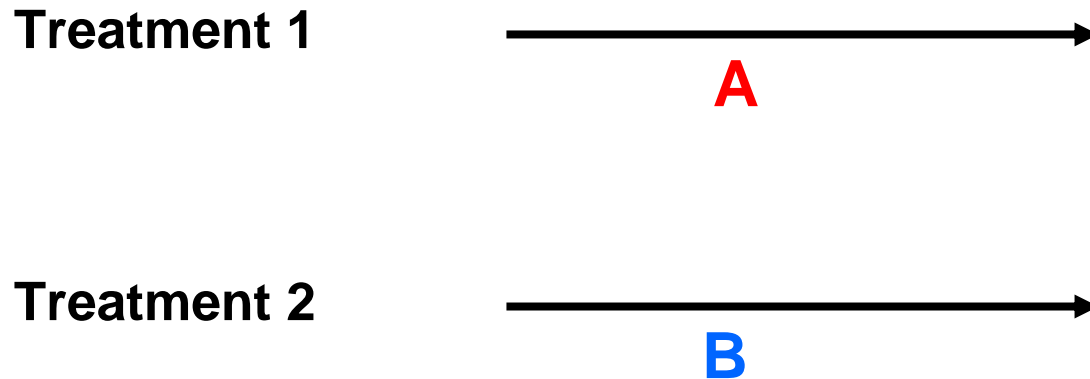
**A**=Test Drug

**B**=RLD



# Other Designs

- **Parallel Design**



- **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  $C_{max}$
  - 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)
  - $f_2$  similarity factor calculation:  $f_2 \geq 50$  is considered similar
- **Setting of dissolution specifications**
  - Immediate release products
  - Delayed release products



Dissolution Methods: Search Results - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites Media Mail Print Send To Favorites

Address [http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp\\_SearchResults\\_Dissolutions.cfm](http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm) Go Links



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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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FDA/Center for Drug Evaluation and Research  
 Office of Generic Drugs  
 Division of Bioequivalence  
 Update Frequency: Quarterly  
 Data Current through: March 22, 2006  
 Last Updated: March 30, 2006

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

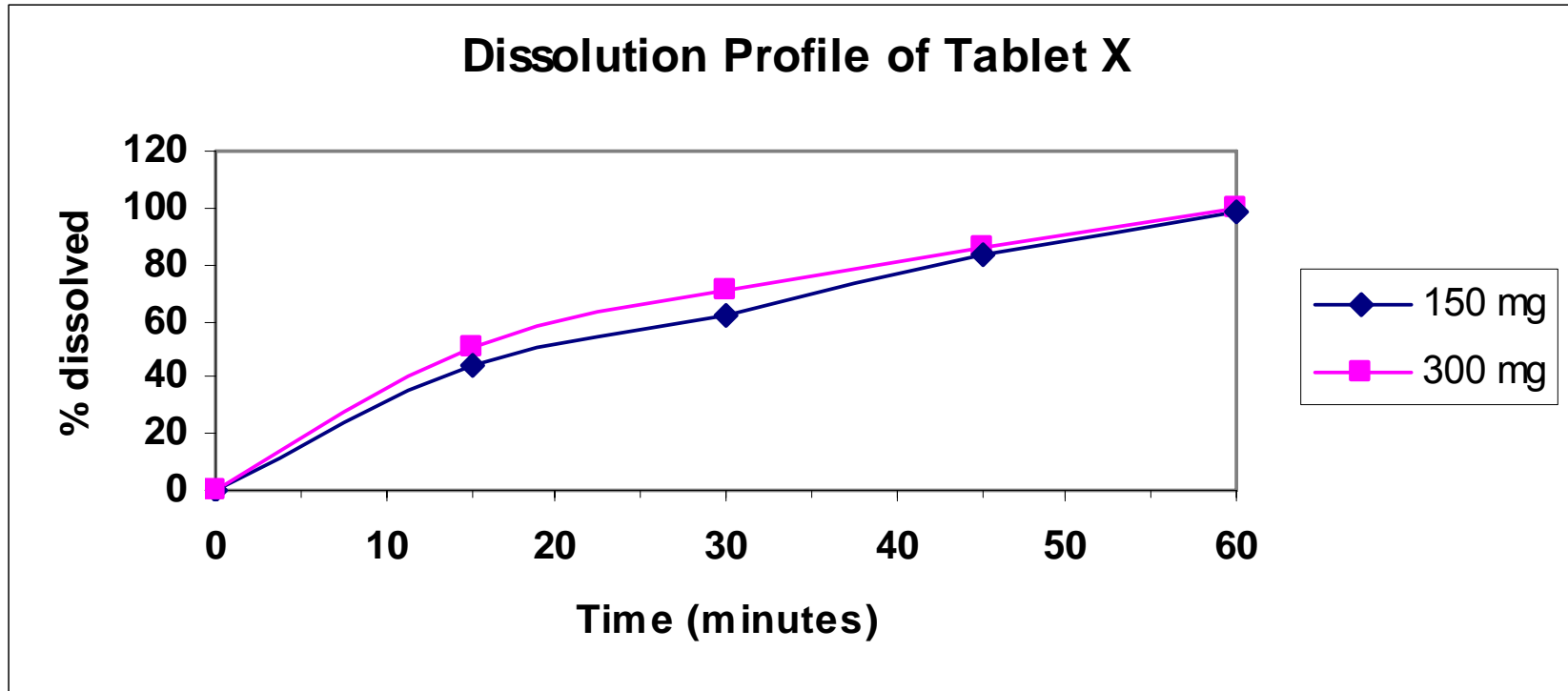


# Formulation Data

Components	150 mg (mg/tab)	300 mg (mg/tab)
<b>Core Components</b>		
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%)
<b>Tablet Core Weight</b>	<b>227.0</b>	<b>454.0</b>
<b>Film Coating Components</b>		
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	--	--
<b>Film coated tablet weight</b>	<b>234.03</b>	<b>468.02</b>



# Dissolution Profile



**f2 = 62.3**





# Additional Information

- [www.fda.gov/cder/ogd](http://www.fda.gov/cder/ogd)
- <http://www.fda.gov/cder/ob/default.htm>



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# Questions

