Regulatory Pathway: Abbreviated New Drug Application

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Unapproved Drugs Workshop

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What are the requirements for a generic drug?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use

Compared to reference listed drug (RLD)
- (brand name product)

Key Point -

In order to submit an ANDA, there must be a reference listed drug (RLD).

Listed drugs are found in FDA's

"Approved Drug Products with Therapeutic Equivalence Evaluations"

(the list; "Orange Book")

Reference products are denoted with a "+" in the Orange Book

APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

22nd EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

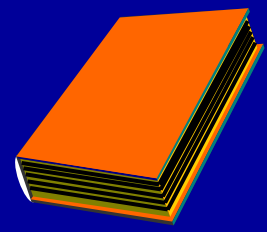
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT & SERVICES

2002

Electronic Orange Book -

http://www.fda.gov/cder/ob/

"Orange Book"



- All FDA approved drug products listed (NDA's, OTC's & ANDA's)
  - Therapeutic equivalence codes
    - "A" = Substitutable
    - "B" = Inequivalent, NOT Substitutable
  - Expiration dates: patent and exclusivity
  - Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare with their proposed products

Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

Current through September 2006**

** In order to provide timely consumer information on generic drugs, the Electronic Orange Book will be updated daily as new generic approvals occur.
Refer to FAQ for additional information. New!!

Annual Edition

FAQ

Search by Active Ingredient Search by Applicant Holder

Search by Proprietary Name Search by Application Number

Search by Patent

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

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

Suitability Petition May Be Option

ANDA for product not identical to listed drug in:

- Route of Administration
- Dosage form
- Strength
- One active ingredient in a combination is substituted with another active
- PREA (21CFR314.93)

505(b)(2) NDAs Another Potential Option

Patent Certifications

The Act requires that an ANDA contain a certification for each patent listed in the Orange Book for the innovator drug. This certification must state one of the following:

I. that patent information relating to the innovator drug has not been filed;

II. that the patent has expired;

III. that the patent will expire on a particular date; or

IV. that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which approval is being sought.

Patent Certifications

- A certification under paragraph I or II permits the ANDA to be approved immediately when otherwise eligible.

- A certification under paragraph III indicates that the ANDA may be approved on the patent expiration date.

Patent Certifications

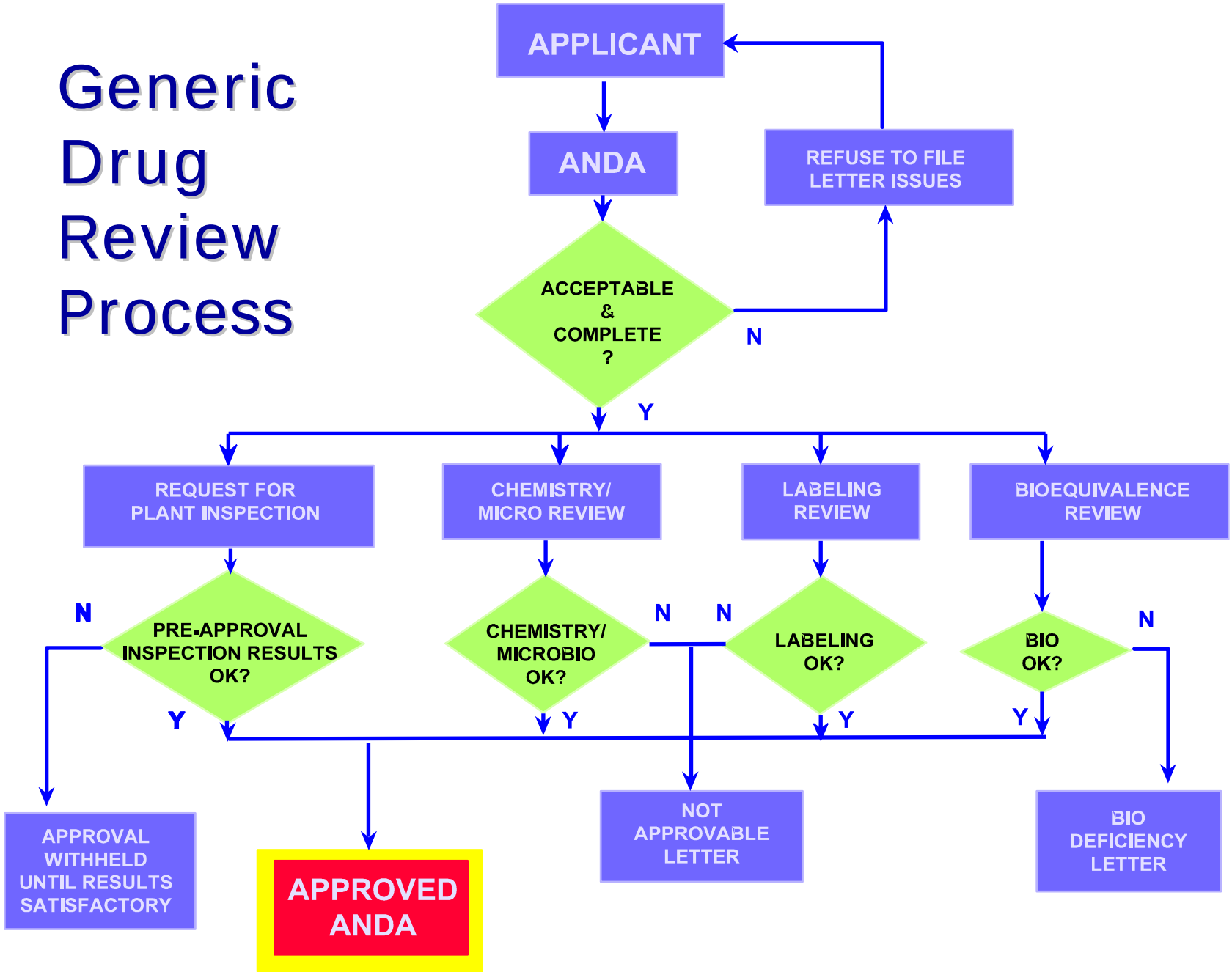
- A paragraph IV certification questions whether the listed patent is valid, enforceable, or will be infringed by the proposed generic product. The ANDA applicant who files a paragraph IV certification to a listed patent must notify the patent owner and the NDA holder for the listed drug that it has filed an ANDA containing a patent challenge. If either party files a patent infringement suit against the ANDA applicant within **45 days** of the receipt of notice, under most circumstances FDA may not give final approval to the ANDA for at least **30 months** from the date of the notice.

- The statute provides an incentive of **180 days** of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification.

NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Generic Drug Review Process



Labeling

- “Same” as brand name labeling
- May delete portions of labeling protected by patent or exclusivity
- May differ in excipients, PK data and how supplied

Chemistry

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specs and tests
- Packaging
- Stability

ANDA Stability and Batch Requirements

- 3 months of accelerated stability data must be submitted with the application
- Available room temperature stability data should also be included. An update on subsequent RT data will be requested during the review process
- One demonstration batch must be manufactured
  - Source of BE study product
  - Source of stability data
  - Complete batch record for this batch must be submitted

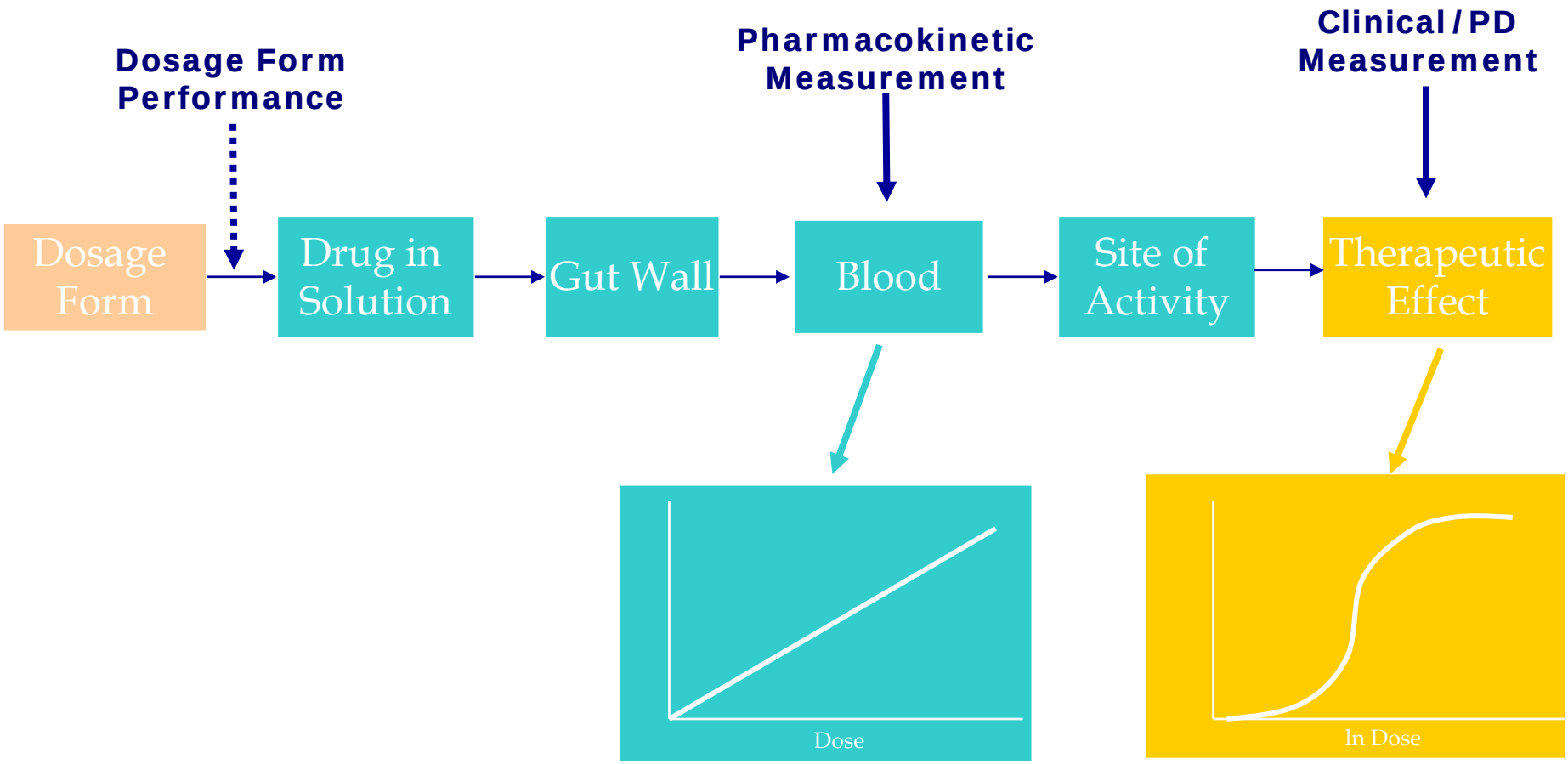
Definition of Bioequivalence

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

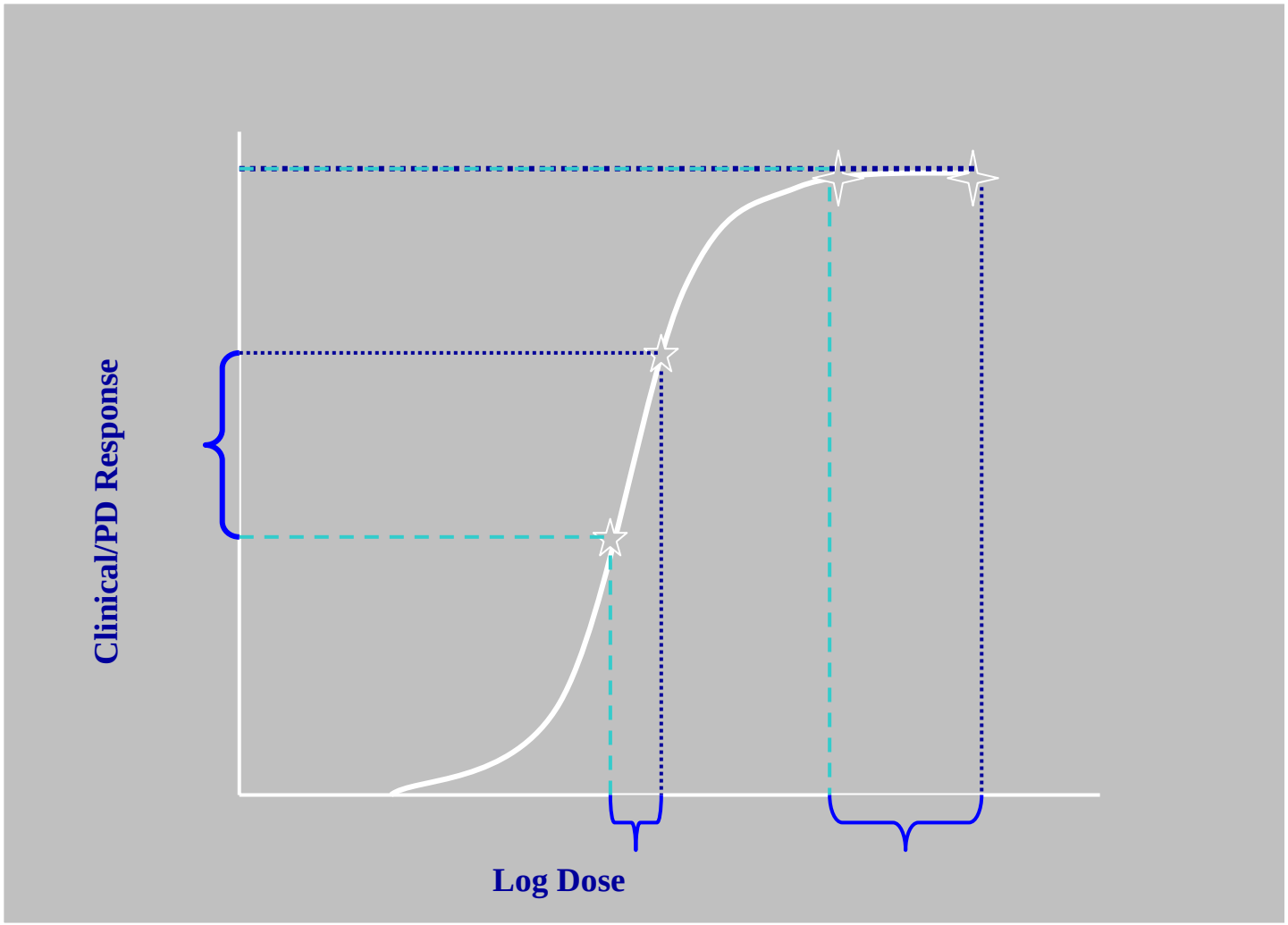
Purpose of BE

- Pharmaceutical equivalence + Bioequivalence = Therapeutic equivalence
- Therapeutically equivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of determining TE is to assure that the formulations perform in an equivalent manner

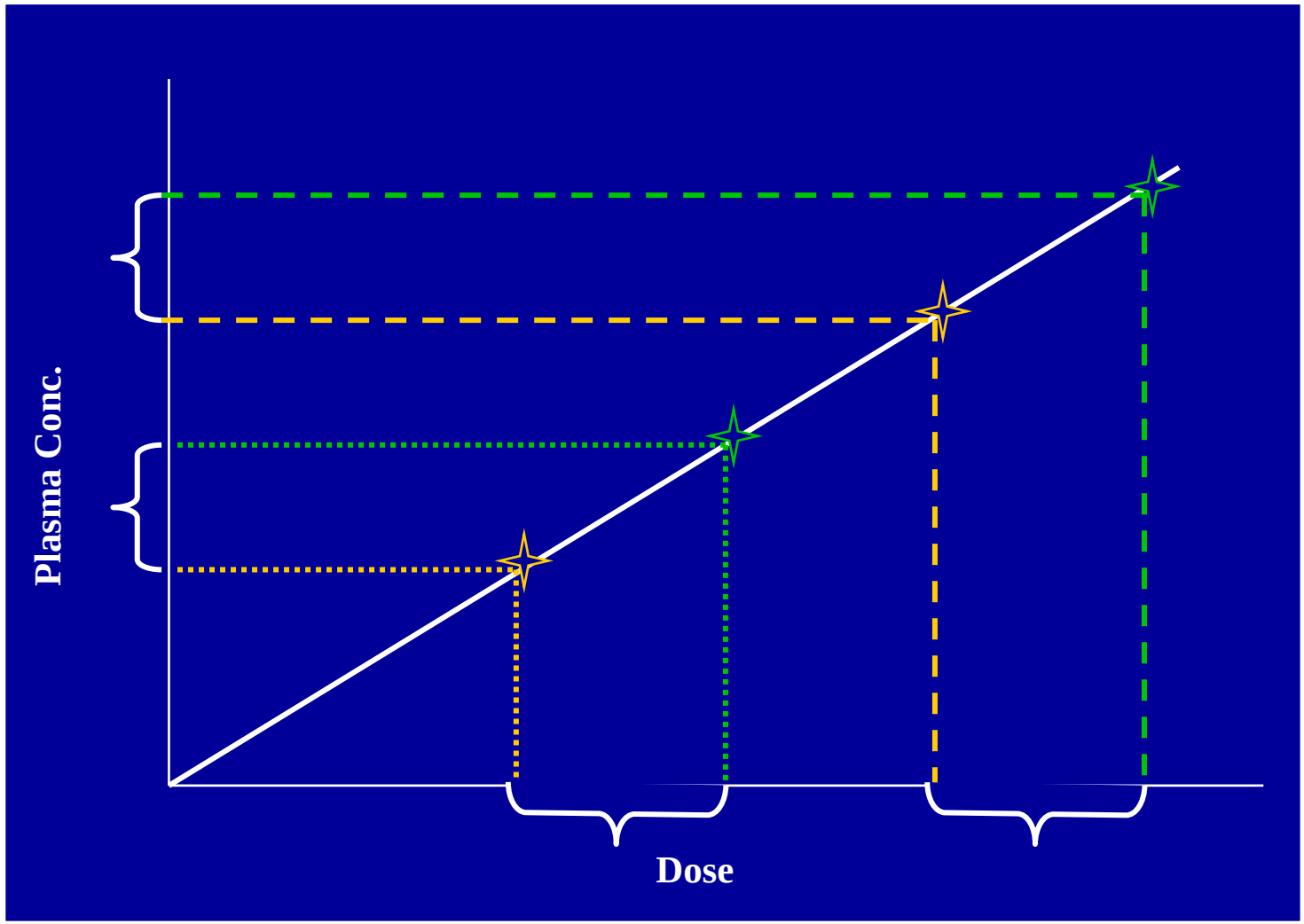
Model of Oral Dosage Form Performance



Clinical/PD Dose-Response



Plasma Concentration-Dose



Study Designs

- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed
- Alternatives
  - Single-dose, parallel, fasted
  - Single-dose, replicate design
  - Multiple-dose, two-way crossover, fasted
  - Clinical endpoint study

Long Half-Life (wash-out)
Amiodarone, Etidronate

Highly Variable Drugs

Less Sensitive
Clozapine (Patient Trials)
Chemotherapy Trials

Topicals
Nasal Suspensions

Waivers of In Vivo Study Requirements

- Definition
- Criteria (21 CFR 320.22)
  - In vivo bioequivalence is self-evident
  - Parenteral solutions
  - Inhalational anesthetics
  - Topical (skin) solution
  - Oral solution
  - Different proportional strength of product with demonstrated BE

Statistical Analysis (Two One-sided Tests Procedure)

- AUC and Cmax
  - 90% Confidence Intervals (CI) must fit between 80%-125%

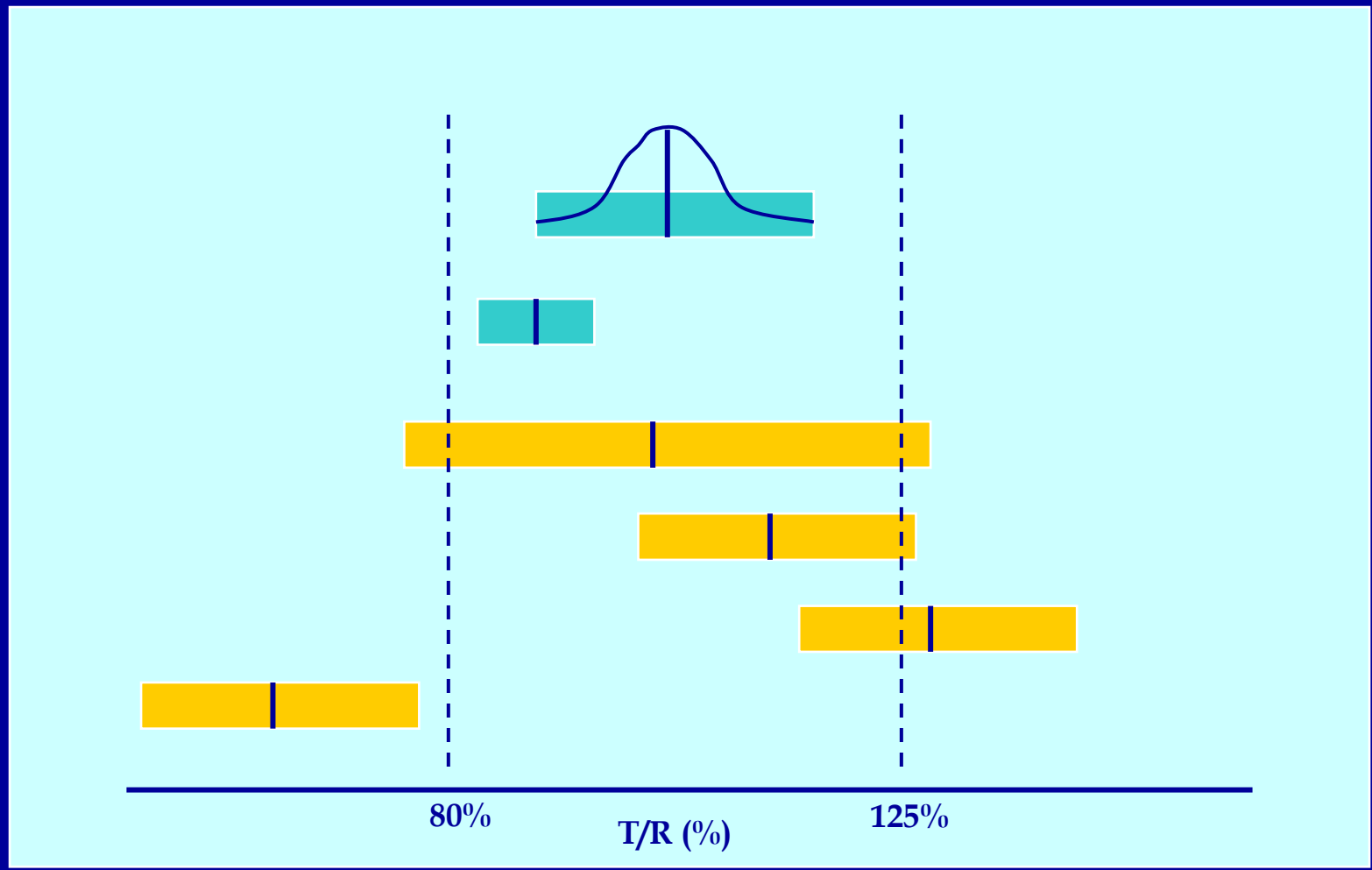
Statistical Analysis

- Bioequivalence criteria
  - Two one-sided tests procedure
    - Test (T) is not significantly less than reference
    - Reference (R) is not significantly less than test
    - Significant difference is 20% (α = 0.05 significance level)
      - T/R = 80/100 = 80%
      - R/T = 80% (all data expressed as T/R so this becomes 100/80 = 125%)

Statistical Analysis 80 - 125 %

- What does this mean?
- Can there be a 46% difference?
- What is a point estimate?
- What is a confidence interval?

Possible BE Results (90% CI)



Resources:

- Regulations
- Guidances
- Generic Pharmaceutical Association
- Several Consultant Firms
- Office of Generic Drugs
- OGD Website: http://WWW.FDA.GOV/CDER/OGD/