仿制药生物等效性研究

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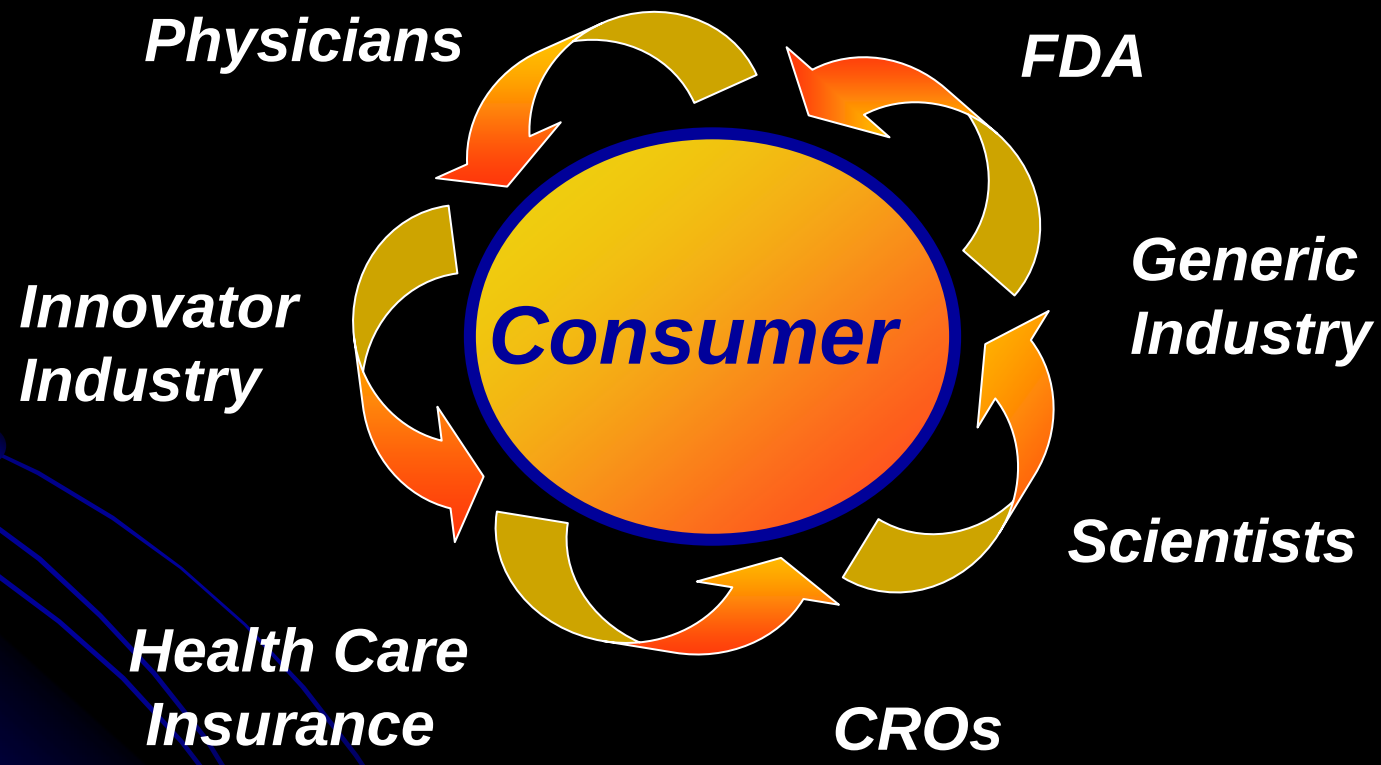
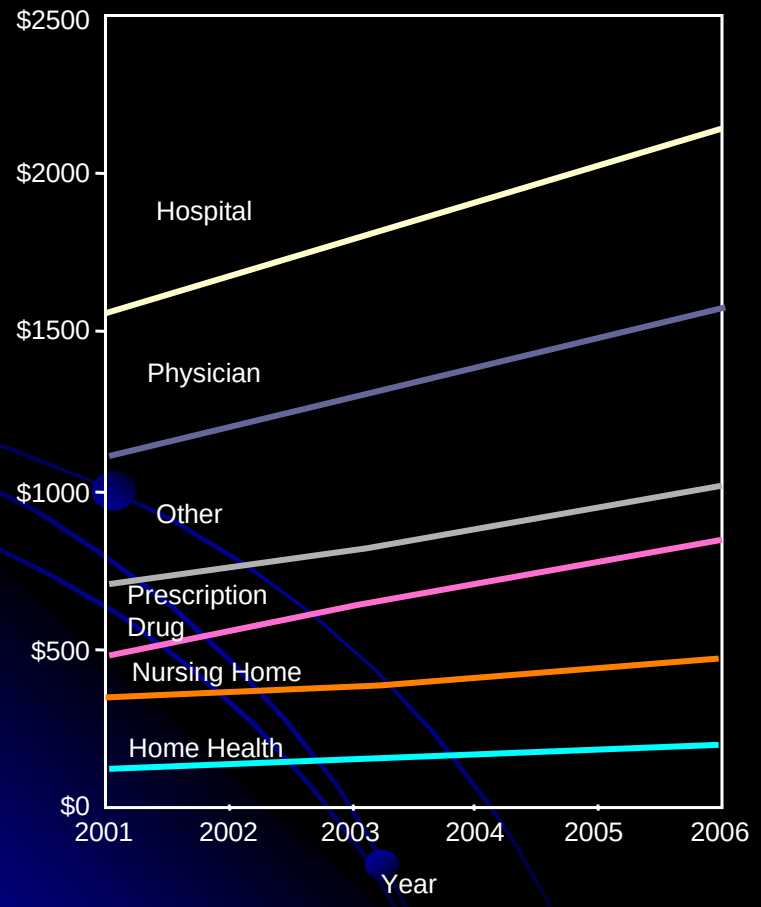
Common Goal
Best Therapeutic Products



Health Care Costs Continue to Increase

US Health Care Expenditures, Per Capita



- Health care costs will increase 44% by 2006
- By 2006, a family of 4 will experience a $2500 increase in annual household medical spending
- Clinicians are increasingly encouraged to help control health care expenses

Diede ML, et al. *Managed Care*. 2002;11:24-33.

Physicians Face Pressure to Prescribe Generic Medications

- Health care decision makers encourage physicians to prescribe generic medications
- Physicians feel increasing pressures are interfering with their ability to prescribe the most effective treatments
- AMA policy: physicians should have the freedom to prescribe generic or brand-name drugs

Jacob J. *Am Med News*. February 18, 2002.

Wilson J. *ACP Observer*. American College of Physicians Web site. Available at: http://www.acponline.org/journals/news/oct97/pressure.htm. Accessed September 29, 2003.

Clinical Relevance of Bioequivalence Issues Substitution Considerations

- Before substituting a generic product, physicians and other decisions makers should consider the potential clinical and pharmacoeconomic consequences
  - Overtreatment
  - Undertreatment
  - Adverse effects
  - Additional expenses
  - Cost savings

Sabatini S, et al. *Am J Kidney Dis*. 1999;33:389-397.

Clinical Relevance of Bioequivalence Issues FDA Recommendations

- To help avoid complications arising from product substitution, the FDA established a list of generic drugs that can be safely and appropriately substituted for brand products
- The FDA does not recommend substituting drugs that have not been determined to be bioequivalent

FDA Policy on Drug Substitution

- The FDA has prepared a list of drugs that are bioequivalent; they can be substituted for each other
- These drugs are listed in a federal publication called *Approved Drug Products With Therapeutic Equivalence Evaluations*, known as the *Orange Book*
- Drugs that are not listed as bioequivalent should not be substituted for each other

FDA Coding of Bioequivalent Products

FDA Coding System

- First letter indicates therapeutic equivalence
  - Yes (A) or no (B)
- Second letter indicates additional information on the basis of FDA evaluation

Coding System First Letter

A Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products

B Drug products not considered to be therapeutically equivalent to other pharmaceutically equivalent products

A-Rated Products

AA

- Bioequivalent products in conventional dosage forms
- Reference (innovator) product has no bioequivalency problems
- No bioequivalency testing performed comparing innovator and generic products
  - Oral dosage form must meet an acceptable in vitro dissolution standard

AB

- Products meeting necessary bioequivalence requirements
- Actual or potential bioequivalence problems have been resolved through appropriate scientific testing

Categories of AB-Rated Products

- When more than 1 referenced product of the same strength exists, a number is added to the AB code
  - AB1, AB2, AB3
- The number designates which generic product is bioequivalent to the reference (innovator) product

Additional A-Rated Products

Rating Label	Type of Drug Product	Characteristics
AN	Solutions and powders for aerosolization	Marketed for use in any of several delivery systems and are considered to be PE and TE; bioequivalence standard is based on in vitro methodology
AO	Injectable oil solutions	Considered to be PE and TE only when the active ingredient, its concentration, and the oil type used as a vehicle are identical
AP	Injectable aqueous solutions and, sometimes, intravenous (IV) nonaqueous solutions	Injectable (parenteral) products that are TE, but may have different characteristics (eg, route of administration)
AT	Topical products	Contain the same active ingredient in the same topical dosage form with a bioequivalence waiver

PE=pharmaceutically equivalent; TE=therapeutically equivalent.

B-Rated Products

BD	Active ingredients and dosage forms with documented bioequivalence problems
BP	Active ingredients and dosage forms with potential bioequivalence problems
BX	Data reviewed by the FDA are insufficient to determine therapeutic equivalence

Drug Products With Special Situations

- Certain drug products have special situations that need more description than a code
  - Problems with standards of identity, analytical methodology, or bioequivalence that are in the process of resolution

Generic Products

- A bioequivalency rating is given to, and designated by, the manufacturer of the generic drug product who originally submitted the abbreviated new drug application
- The drug distributor provides the drug product to a wholesale company or a pharmacy
- Generic prescriptions may be filled with the most cost efficient generic product

Hubbard WK. *Fed Regist*. 1997;620:43535-43538.

What are the requirements for a generic drug?

- Labeling
- Chemistry/Microbiology
- Bioequivalence
- Legal

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

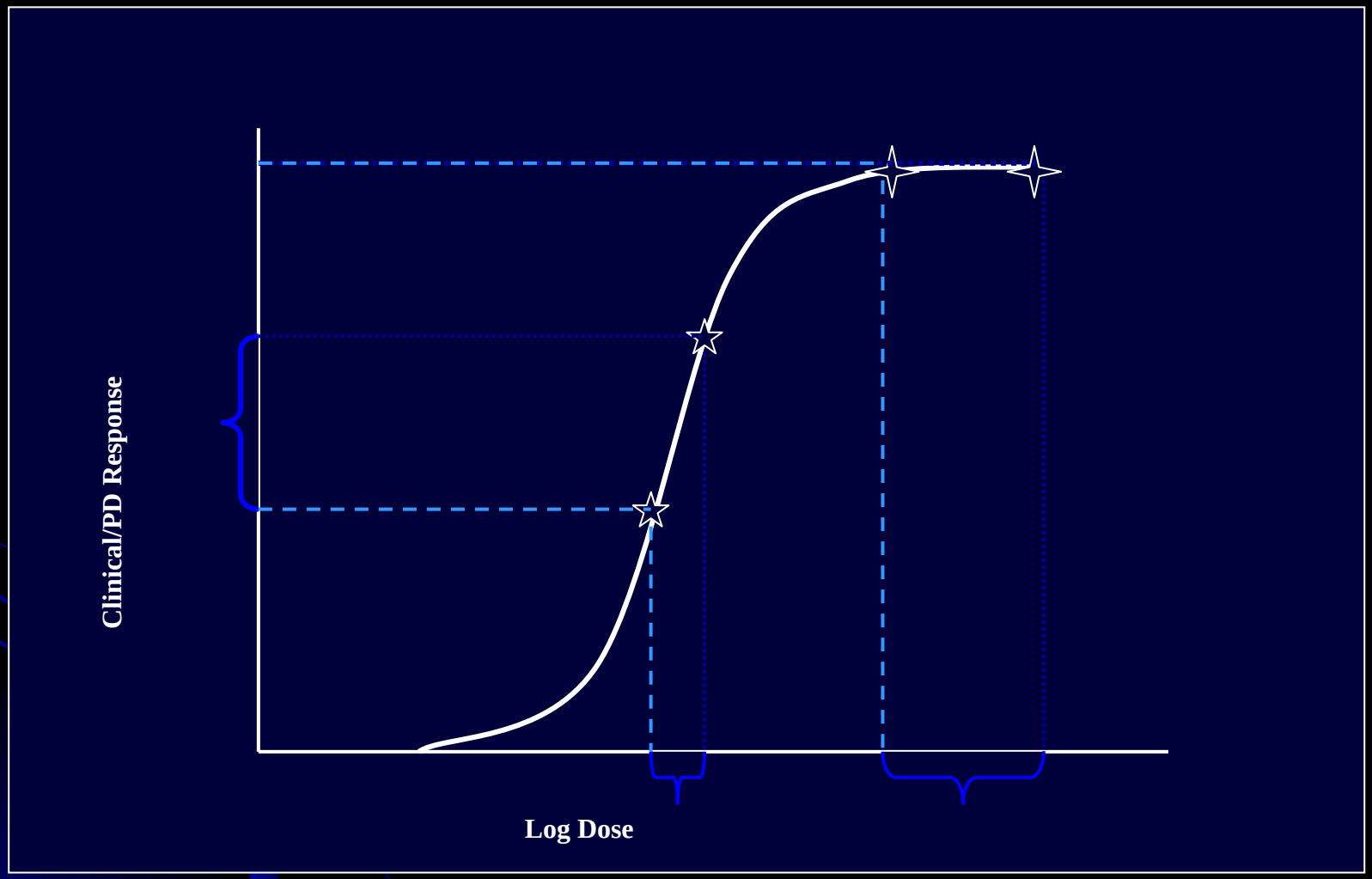
Chemistry

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

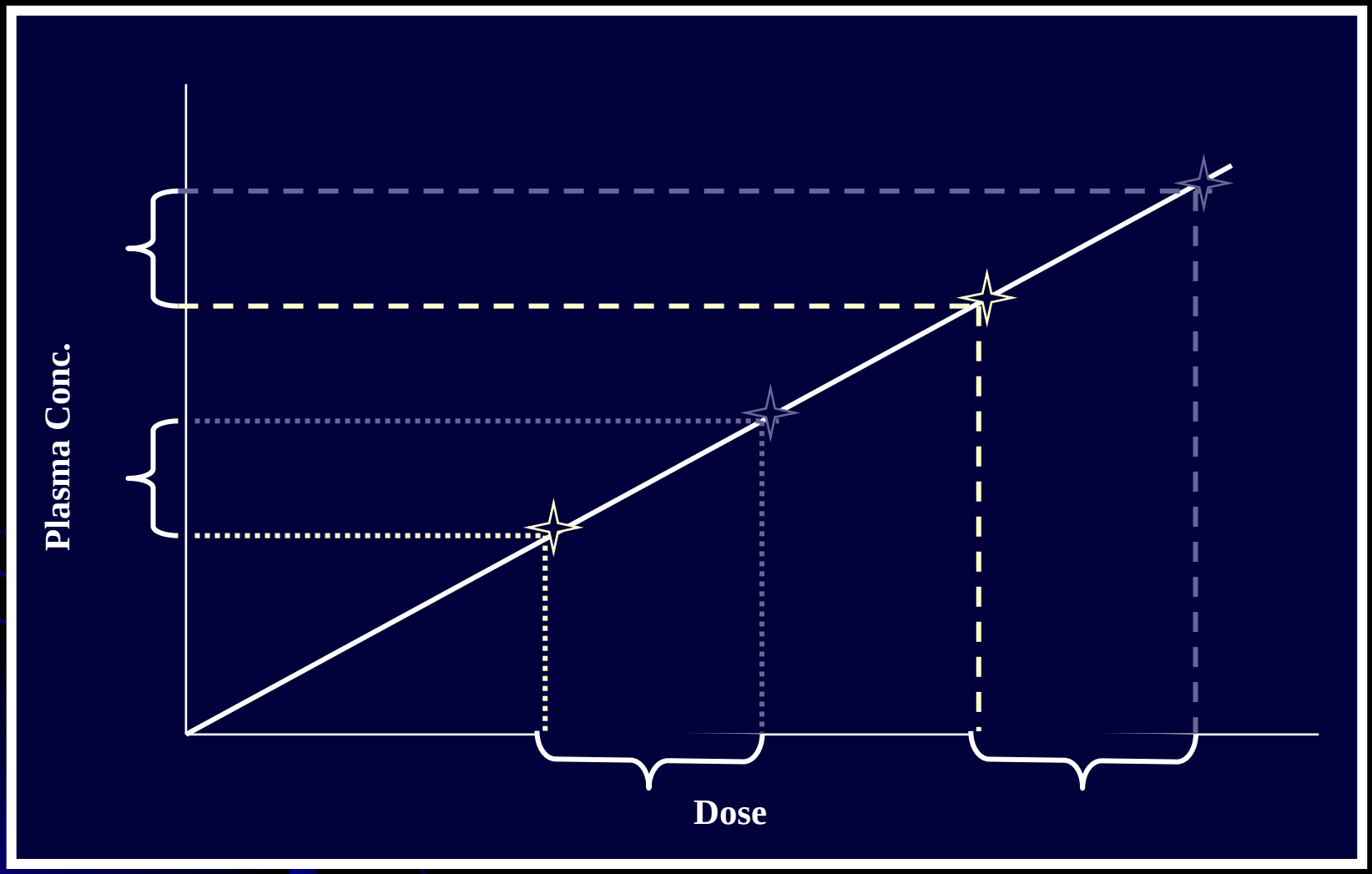
Manufacturing Compliance Programs

- Purpose - To assure quality of marketed drug products
- Mechanisms - Product Testing
  - Surveillance
  - Manufacturing/Testing plant inspections
  - Assess firm’s compliance with good manufacturing processes

Clinical/PD Dose-Response



Plasma Concentration-Dose

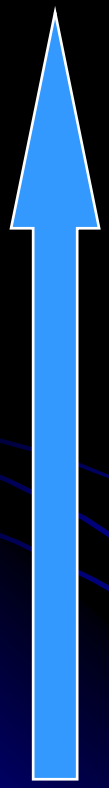


FDA Definitions Used in Bioequivalence Determinations

FDA Determinations of Bioequivalence Main Terms

- Pharmaceutical equivalents
- Pharmaceutical alternatives
- Therapeutic equivalents
- Bioequivalence
- Bioavailability

生物等效性的测定方法 (21 CFR 第320.24节)



- 生物体液中活性成分的体内测试
- 体内药效对照法
- 体内有限的临床对照法
- 体外方法
- FDA认可的其它方法

Pharmaceutical Equivalents

- Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), have the same dosage form and route of administration, and are identical in strength or concentration
- Equivalent products contain the same amount of ingredient in the same dosage form but may differ in characteristics, such as shape, release mechanisms, and packaging

Pharmaceutical Alternatives

- Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, are different salts, esters, or complexes of the same moiety, are different dosage forms, or are different strengths
- Other pharmaceutical alternatives
  - Different dosage forms and strengths within a single product line by a single manufacturer
  - Extended-release formulations when compared with immediate- or standard-release formulations

Therapeutic Equivalents

- Drug products are considered therapeutic equivalents if they are all of the following
  - Pharmaceutical equivalents
  - Bioequivalent
  - Approved as safe and effective
  - Adequately labeled
  - Manufactured in compliance with current Good Manufacturing Practice regulations
- Therapeutic equivalents are expected to have the same clinical effect and safety profile

Bioequivalence

- Drug products are considered bioequivalent if they are 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
- Bioequivalence may be demonstrated through in vivo or in vitro test methods, comparative clinical trials, or pharmacodynamic studies

Determining Bioequivalence: FDA Guidelines

Bioavailability

- Bioavailability is the rate and extent to which the active ingredient in pharmaceutical equivalents becomes available at the site of drug action
- Bioavailability may be assessed by measurements intended to reflect this rate and extent

Use of Bioequivalence to Determine Therapeutic Equivalents

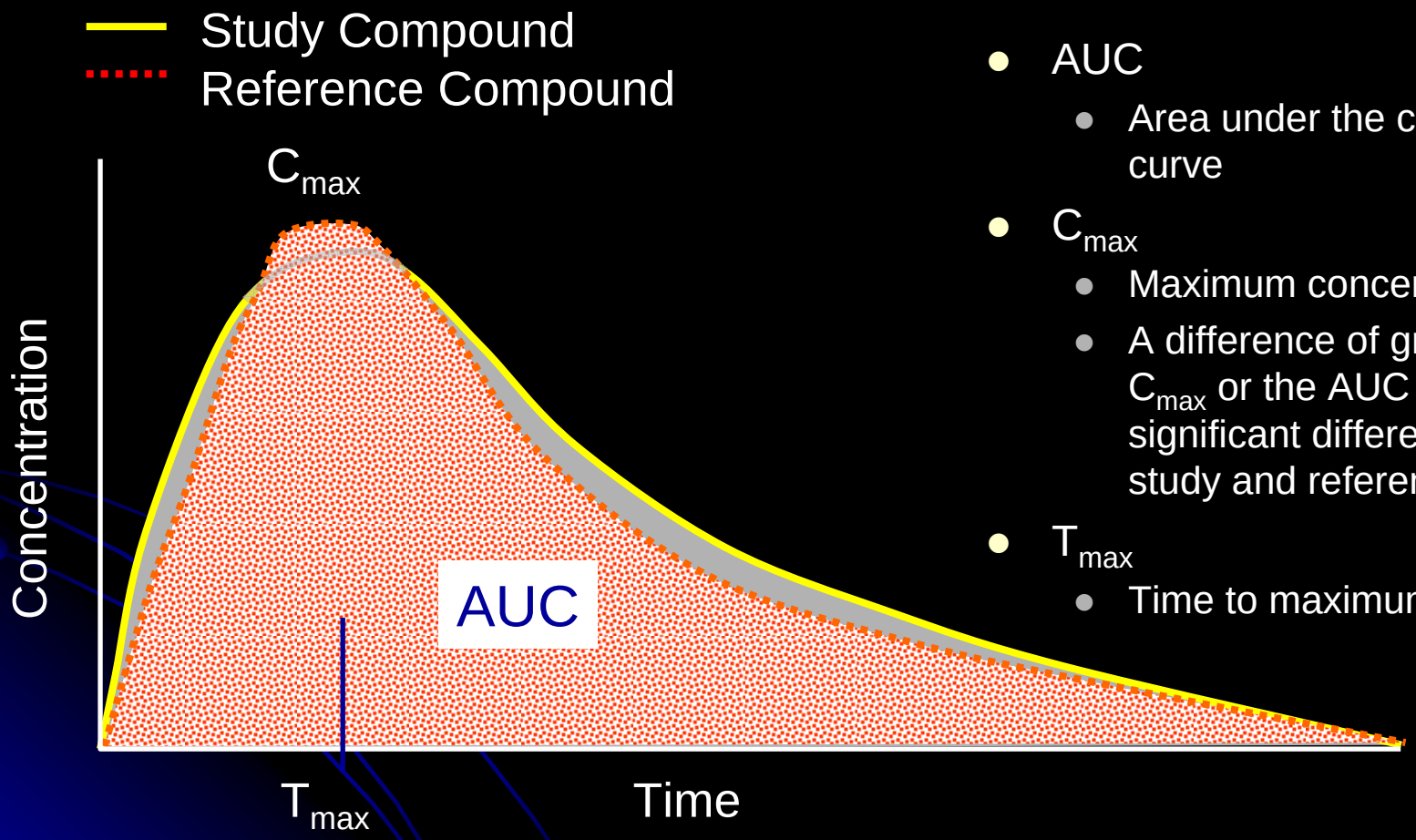
- There is a strong correlation between single-dose pharmacokinetics and therapeutic effects
- Single-dose pharmacokinetics are similar to steady-state pharmacokinetics
- Patients have a pharmacokinetic profile comparable to that of healthy volunteers
- A –20% to +25% difference in absorption (C_{max}, AUC) has no effect on therapeutic outcomes

FDA Methods to Determine Bioequivalence

- Generic drug manufacturers must demonstrate that a drug is bioequivalent to a reference drug product
- In order of FDA preference, methods used to define bioequivalence
  - Pharmacokinetic studies
  - Pharmacodynamic studies
  - Comparative clinical trials
  - In vitro studies

Food and Drug Administration. Code of Federal Regulations. Title 21, Part 320: Bioavailability and Bioequivalence Requirements. Section 320.24. 2003. Available at: http://www.accessdata.fda.gov. Accessed September 29, 2003.

Pharmacokinetic Studies
Key Measurements



- AUC
  - Area under the concentration- time curve
- C_{max}
  - Maximum concentration
  - A difference of greater than 20% in C_{max} or the AUC represents a significant difference between the study and reference compounds
- T_{max}
  - Time to maximum concentration

统计分析(双单侧T检验程序)

- AUC 与 C_{max}
- 对数转换数据
- 多因素方差分析(ANOVA)
  - 模型: 阶段、服药顺序、药剂(顺序)、疗法
- 90%置信区间(CI)

生物等效性标准

- 显著差异为 20% (显著性水平α=0.05)
- 两个单因素检测程序
  - ✓ 测试药物(T)不显著低于参比药物： T/R 的90%置信区间不小于 80%
  - ✓ 参比药物(R)不显著高于测试药物： R/T的90%置信区间不大于 125%
- 接受的标准: T/R 的90%置信区间为**80.00-125.00%**
  - ✓ $LnAUC_t$
  - ✓ $LnAUC_{inf}$
  - ✓ LnC_{max}

Pharmacokinetic Studies
Healthy Volunteers Versus Patients

- If two drug products perform the same in healthy volunteers, the assumption is made that they will perform the same in patients with the disease, except in the case of some drugs that are potentially toxic

Welage LS, et al. *J Am Pharm Assoc.* 2001;41:856-867.

FDA Recommendations for BE Study Design

- Crossover study design (non-replicate preferred)
- Administer product with 8 oz water under fasting conditions
  - Control water intake 1 hour before and after drug administration
- Meal provided no less than 4 hours after drug administration
- No alcohol 24 hours prior to study implementation and until after last sample taken
- Blood samples (12 to 18 samples, including a pre-dose measurement)

FDA Recommendations for BE Study Design

- Adequate washout period (more than 5 half-lives)
- Single dose studies are recommended; if used, multiple dose studies should assess steady state levels

Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison → FeV_1 Albuterol; Blanching Study; Topical Corticosteroid
- In vivo limited clinical comparison
- In vitro comparison → Topicals; Nasal Suspensions
- Any other approach deemed appropriate by FDA → Questran - Binding Studies; Nasal Solutions-Sprayer Evaluation; Propofol - Droplet Size

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
80 - 125 %

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

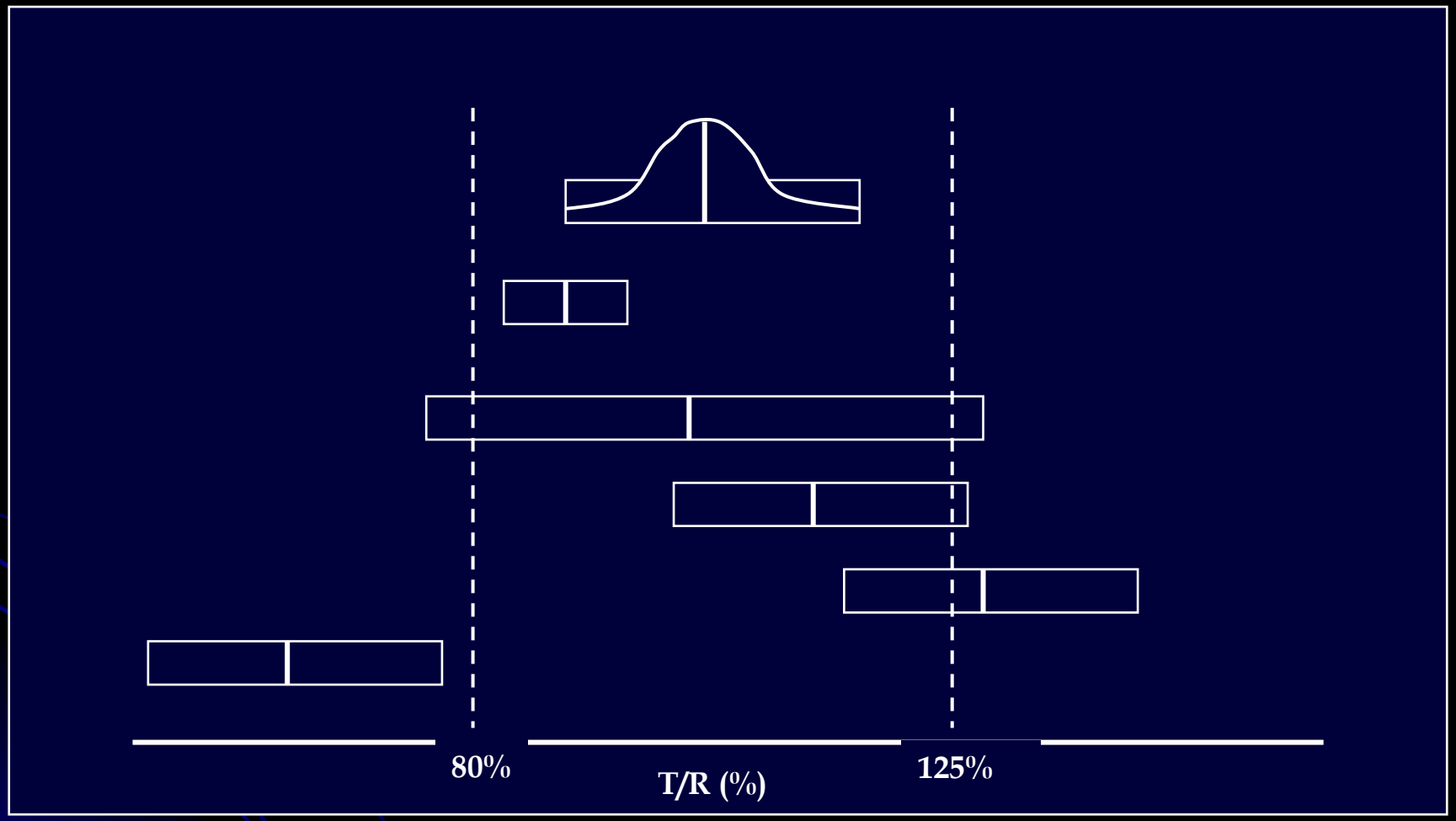
Statistical Analysis

- 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%)

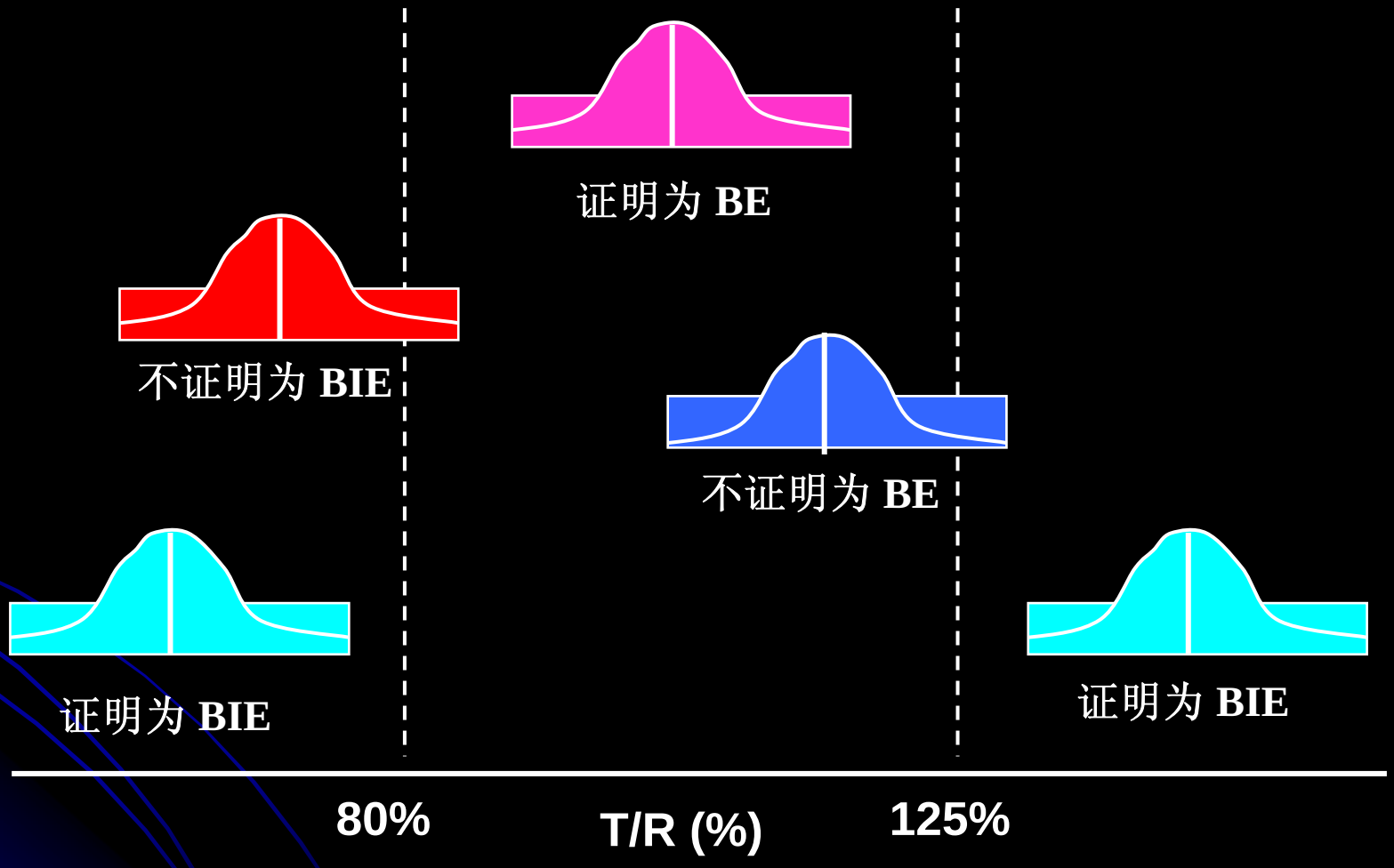
Example

Drug A Tablets Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 12345				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng.hr/ml)	6926.21	7073.05	**0.98**	**88.52-108.32**
AUC∞ (ng.hr/ml)	7272.94	7442.56	**0.98**	**88.79-107.55**
Cmax (ng/ml)	1014.78	1067.66	**0.95**	**87.18-103.62**

Possible BE Results (90% CI)

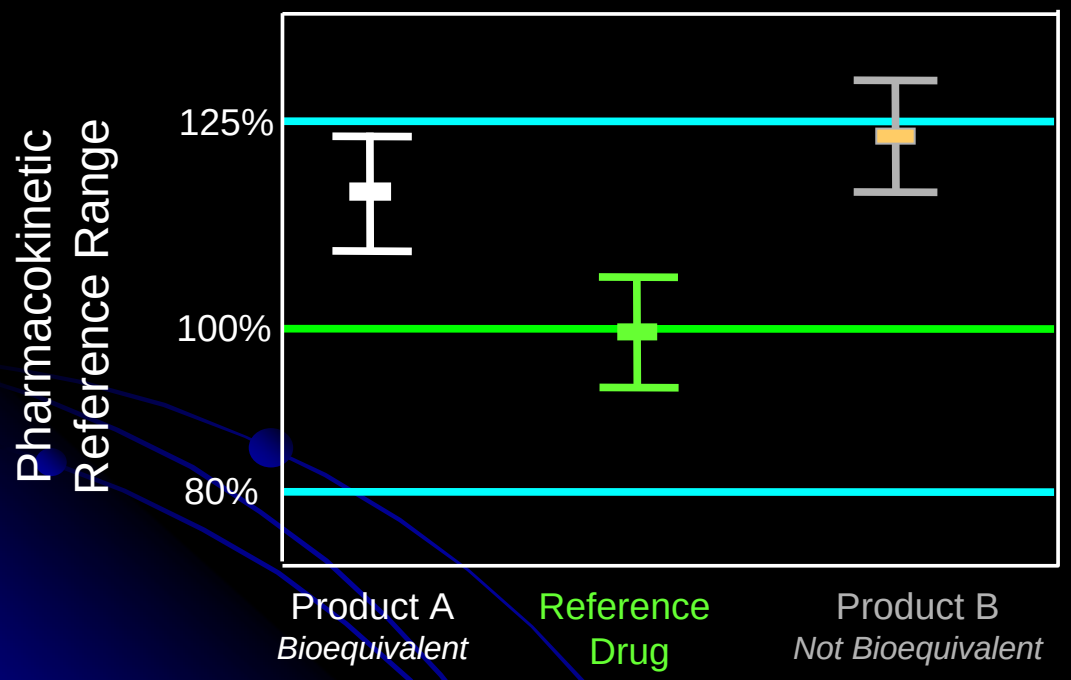


可能的生物等效性研究结果



BE = 生物等效， **BIE** = 生物不等效

FDA Requirements for Bioequivalence



- Product A is bioequivalent to the reference drug; its 90% confidence interval of the AUC falls within 80% to 125% of the reference drug
- Product B is not bioequivalent to the reference drug; its 90% confidence interval of the AUC falls outside of 80% to 125% of the reference drug

Products With a Narrow Therapeutic Range

Narrow Therapeutic Range Definition

- The FDA defines a drug as having a narrow therapeutic range if
  - There is less than a 2-fold difference between median lethal dose and median effective dose values
  - There is less than a 2-fold difference between minimum toxic concentrations and minimum effective concentrations in the blood
  - Safe and effective use of the drug products require careful titration and patient monitoring

Narrow Therapeutic Range Regulatory View

- For drugs containing certain substances subject to therapeutic drug concentration monitoring and/or where product labeling indicates a narrow therapeutic range designation, standard BE criteria will be used with the recommended limits of 80% to 125%

Narrow Therapeutic Range
Clinical View

- A 20%-25% potential difference in bioavailability would alter therapeutic effects
- Current FDA bioequivalence and therapeutic equivalent evaluation guidelines may not be appropriate for assessment of narrow therapeutic range drugs

Determining the Bioequivalence of Levothyroxine Sodium Products

Levothyroxine Sodium Characteristics

- Sodium salt of the levo isomer of thyroxine
- Orally administered levothyroxine sodium is used as replacement therapy
  - Has a narrow therapeutic range
    - No 2-fold difference in the median lethal dose or concentration
  - Difficult to assess the bioavailability
    - A supraphysiologic dose (600 μg) needs to be given in PK studies
    - Has a long half-life (7 days)

FDA Guidelines for Levothyroxine Sodium Bioequivalence Studies

- Pharmacokinetic study
- Crossover design
- At least 24 healthy adult volunteers
- Single 600 μg dose, fasting
- Thyroxine plasma level measurement with 90% confidence interval
- Monitoring for 48 hours
- No TSH measurement required
  - Recommended in dose proportionality studies

Pharmacokinetics or Pharmacodynamics to Evaluate Bioequivalence and Therapeutic Equivalents

- Regulatory view
  - Pharmacokinetic data are readily measurable, accurate, and have been used to evaluate thousands of products
- Clinician's view
  - Thyroid-stimulating hormone is the pharmacodynamic end point used in the clinic
  - Pharmacokinetic data may not be relevant to clinical outcomes

Most Levothyroxine Sodium Products Are Not Interchangeable

Unithroid

Levoxyl

Levo-T

Thyro-Tab

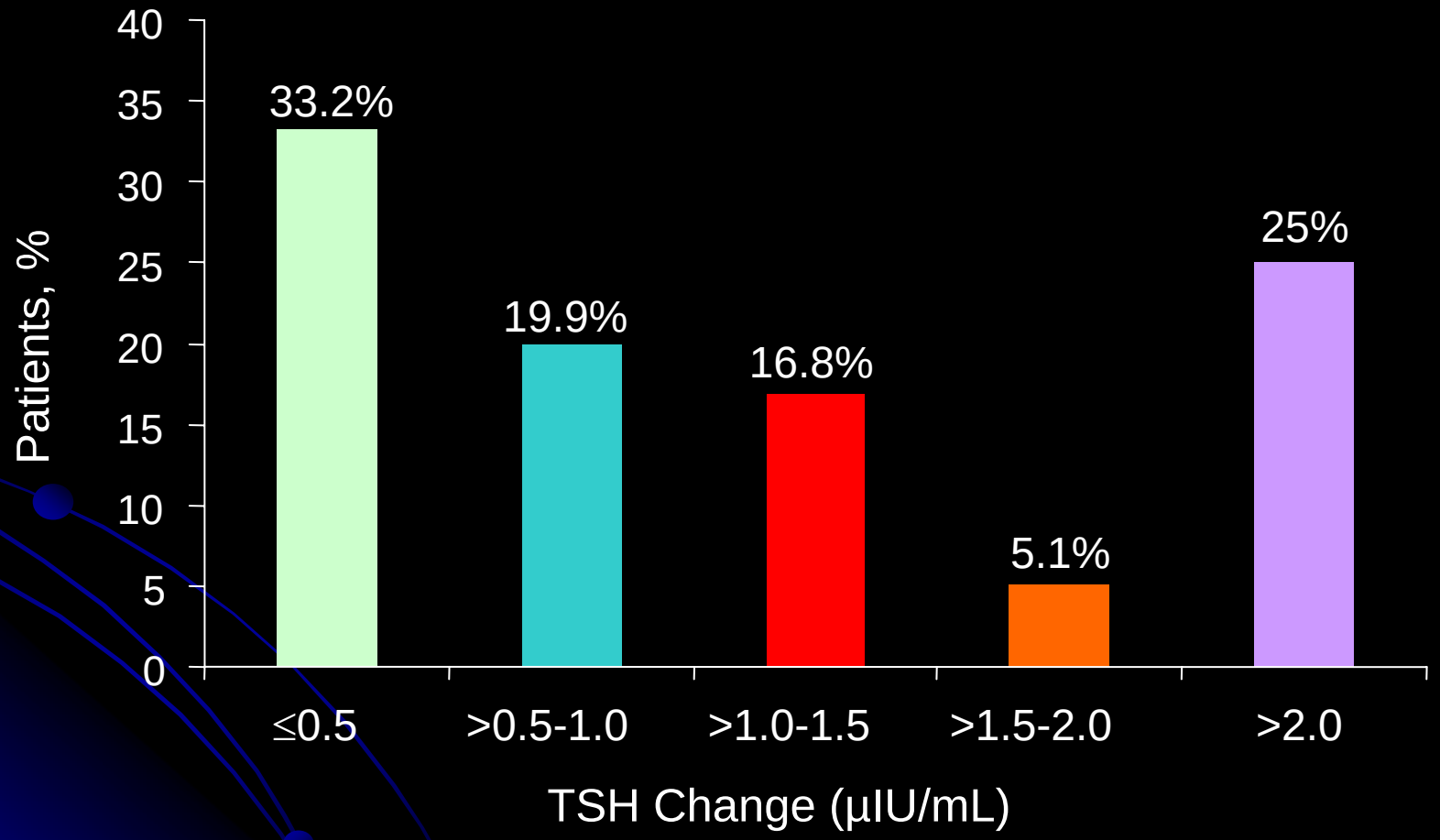
Novothyrox

Synthroid

Only 1 generic levothyroxine sodium product has been compared with a branded product

- Only 1 generic levothyroxine sodium product is AB-rated and bioequivalent to Unithroid
- All branded levothyroxine sodium products are BX-rated and are not interchangeable

TSH Change Following a Change in Levothyroxine Sodium Product



Data on File. Abbott Laboratories. 2003.

Levothyroxine Sodium Product Substitution

- The American Thyroid Association and The Endocrine Society
  - "Patients could be harmed medically if they were forced to switch from one brand to another without appropriate monitoring and, when needed, dose adjustment."
- American Association of Clinical Endocrinologists
  - "Small differences between doses…can have major clinical implications for thyroid patients, including atrial fibrillation, osteoporosis, and uncontrolled hypercholesterolemia."

State Regulatory Environment Definitions

- Individual state determination
  - Product interchange decisions are based on individual state formularies
  - Levothyroxine sodium products are not on the interchangeable formulary in any state
- *Orange Book*
  - Substitution is permitted only if products have been determined to be AB-rated in the *Orange Book*
  - All levothyroxine sodium products listed as BX-rated are not interchangeable
- Professional judgment
  - Pharmacists are allowed to use their professional judgment to make determinations on interchangeable products
  - Substitution policy is based on references such as the US Pharmacopeia, American Hospital Formulary, and peer-reviewed data

Economic Consequences of Levothyroxine Sodium Product Substitution

- Savings on prescription costs could be outweighed by costs associated with monitoring for retitration and/or adverse effects

Office revisit	$45 to $130
TSH retest	$20 to $45
Follow-up re-evaluation and retest in 6 weeks	$45 to $130
Additional treatment time needed to get hypothyroidism under control	Additional costs likely

Conclusions

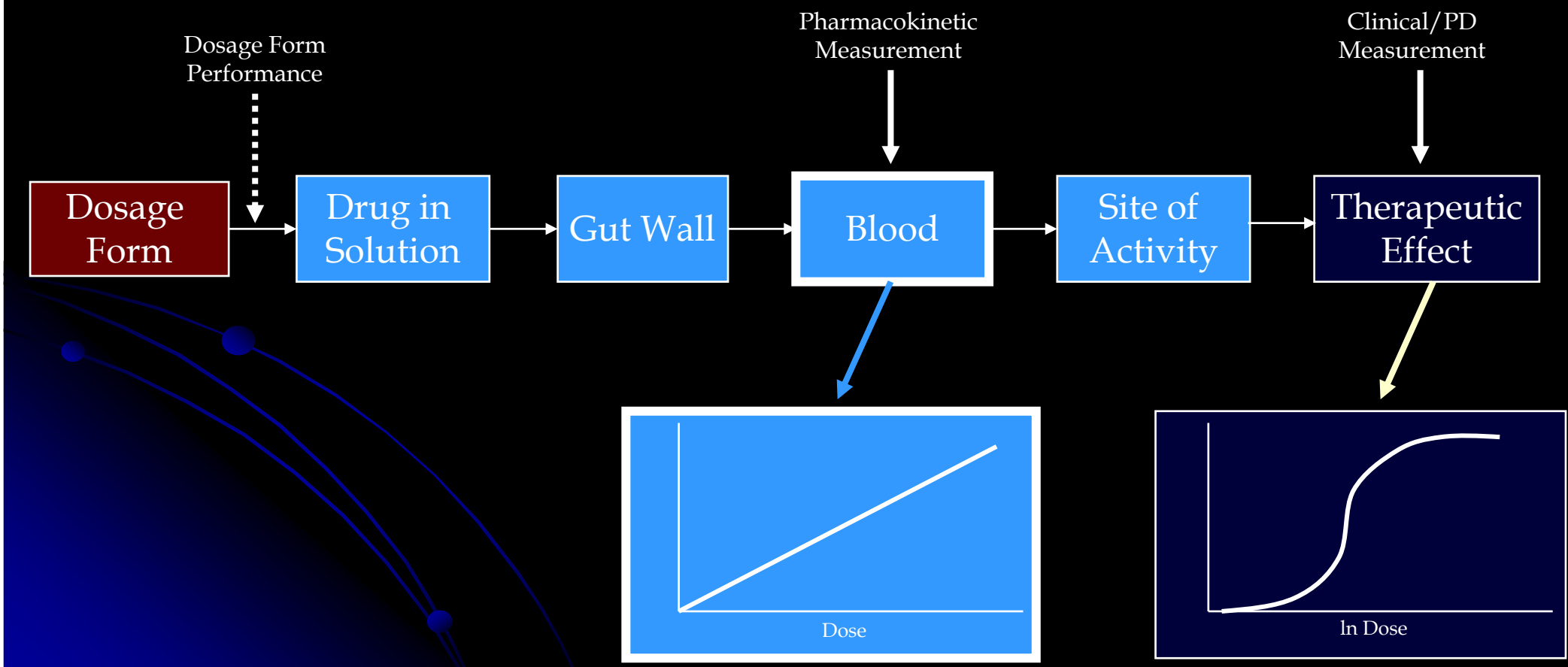
- Levothyroxine sodium product substitution after a patient achieves a steady state can lead to the development of hyperthyroidism or hypothyroidism
- Levothyroxine sodium product substitution may increase the chance of developing adverse health outcomes other than thyroid dysfunction
- Levothyroxine sodium product substitution may increase physician and pharmacist workload
- There may be no economic benefit to levothyroxine sodium product substitution

Dermatopharmacokinetics (DPK)

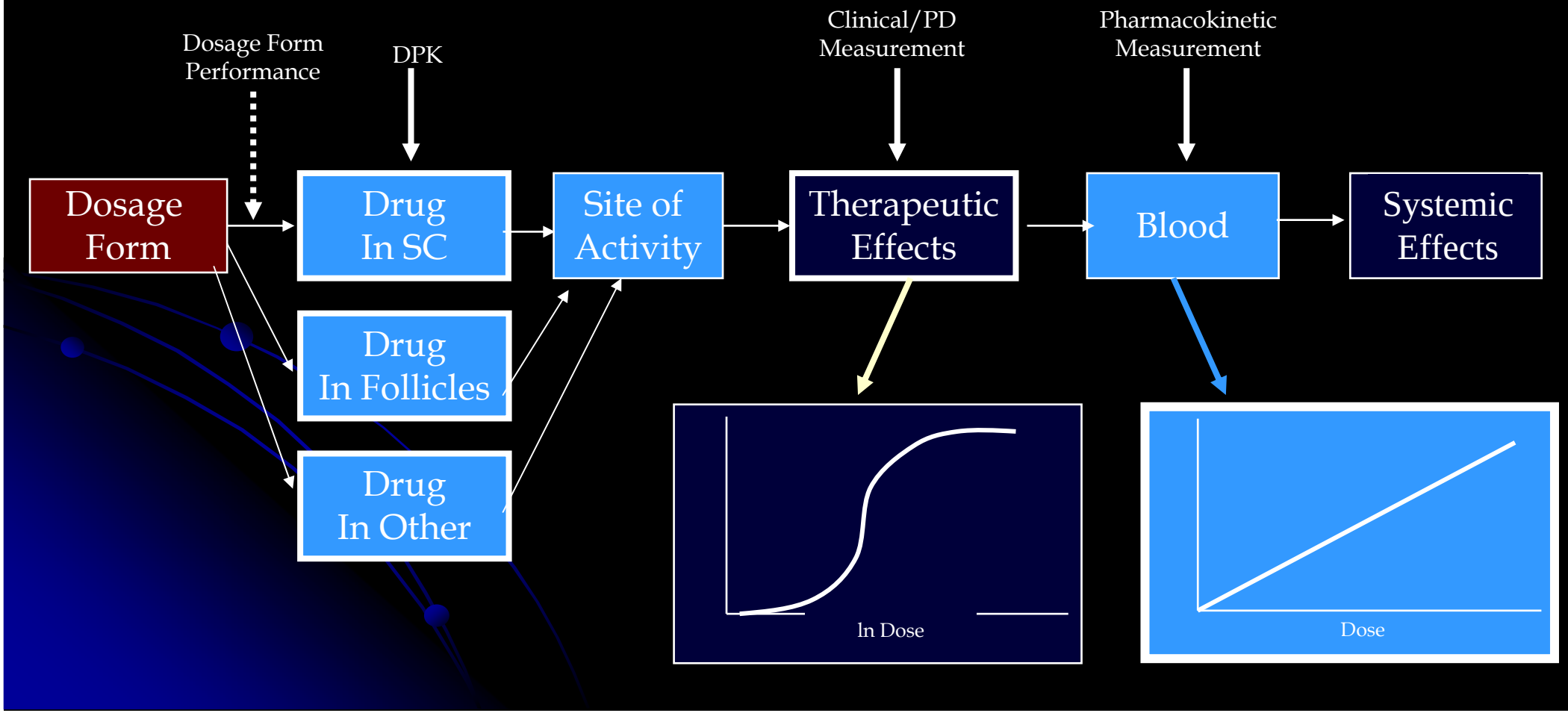
Purpose of BE

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring.
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner.

Model of Oral Dosage Form Performance



Model of Topical (Skin) Dosage Form Performance



Current Methods BE Methods for Topical Products

- BE Study with Clinical End-points
  - Expensive
  - Insensitive to differences in formulation performance
- BE Study with Pharmacodynamic End-points
  - Limited to only a few classes of compounds (glucocorticoids)
- In Vitro Drug Release

Description of DPK Method

- Theory
  - Pharmacokinetic approach applied to drug concentrations in stratum corneum (SC)
- Method
  - Tape stripping is used to remove successive layers of SC after topical drug administration
  - Uptake and elimination from SC are determined
  - Differences in formulation performance (BE) are determined at the same time in the same individual

Hypothesis

The dermatopharmacokinetic (DPK) method will assess the BIOEQUIVALENCE of three 0.025% tretinoin gel products similar to the Clinical Efficacy / Safety Trial method

Tretinoin gel, 0.025%

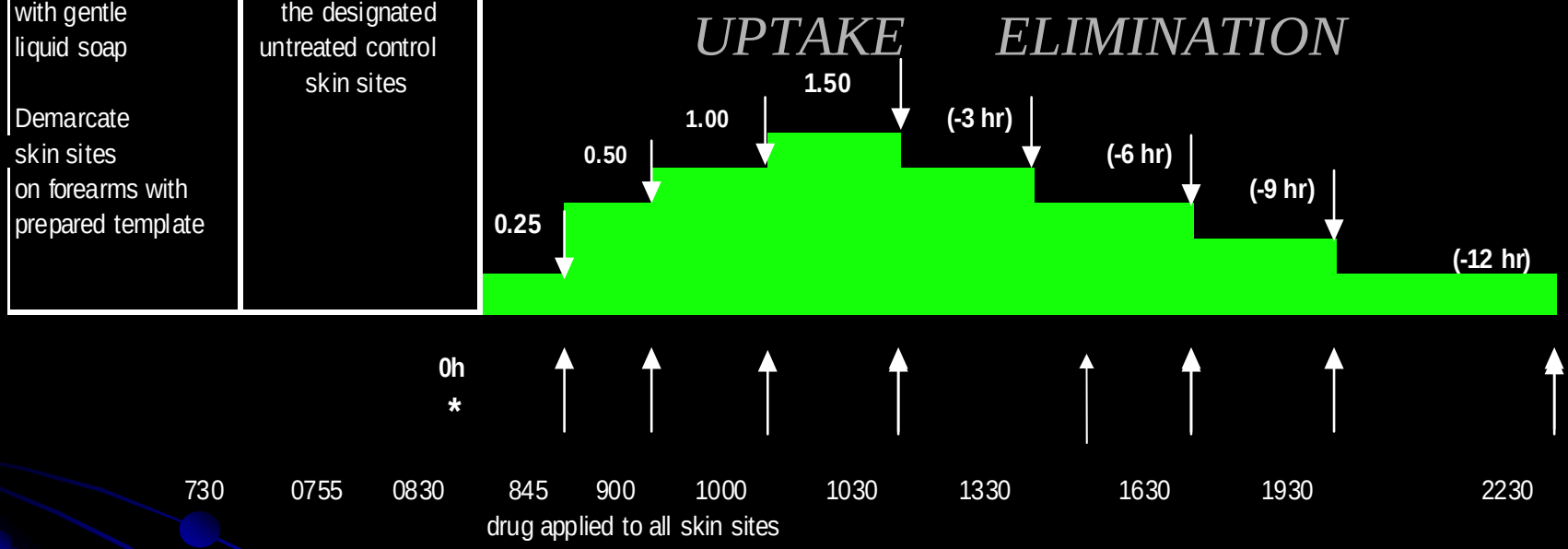
A Ortho Reference	B Bertek Test 1	C Spears Test 2
Butylated hydroxy toluene	Butylated hydroxy toluene	Butylated hydroxy toluene
Hydroxypropyl cellulose	Hydroxypropyl cellulose	Hydroxypropyl cellulose
Alcohol 90% (w/w)	Polyolprepolymer-2 Ethanol 83% (w/w) Denatured with *tert*-butyl alcohol and brucine sulfate	Alcohol 90% (w/w)

Bioequivalence Assessment
Clinical Efficacy/Safety Acne Trial

Clinical Parameter	Ortho vs. Spear Q1 Q2 similar	Ortho vs. Bertek Q1 Q2 different
Efficacy	BE	Not BE Ortho > Bertek
Safety	BE	Not BE Bertek 2X > Ortho

DPK Experimental Design

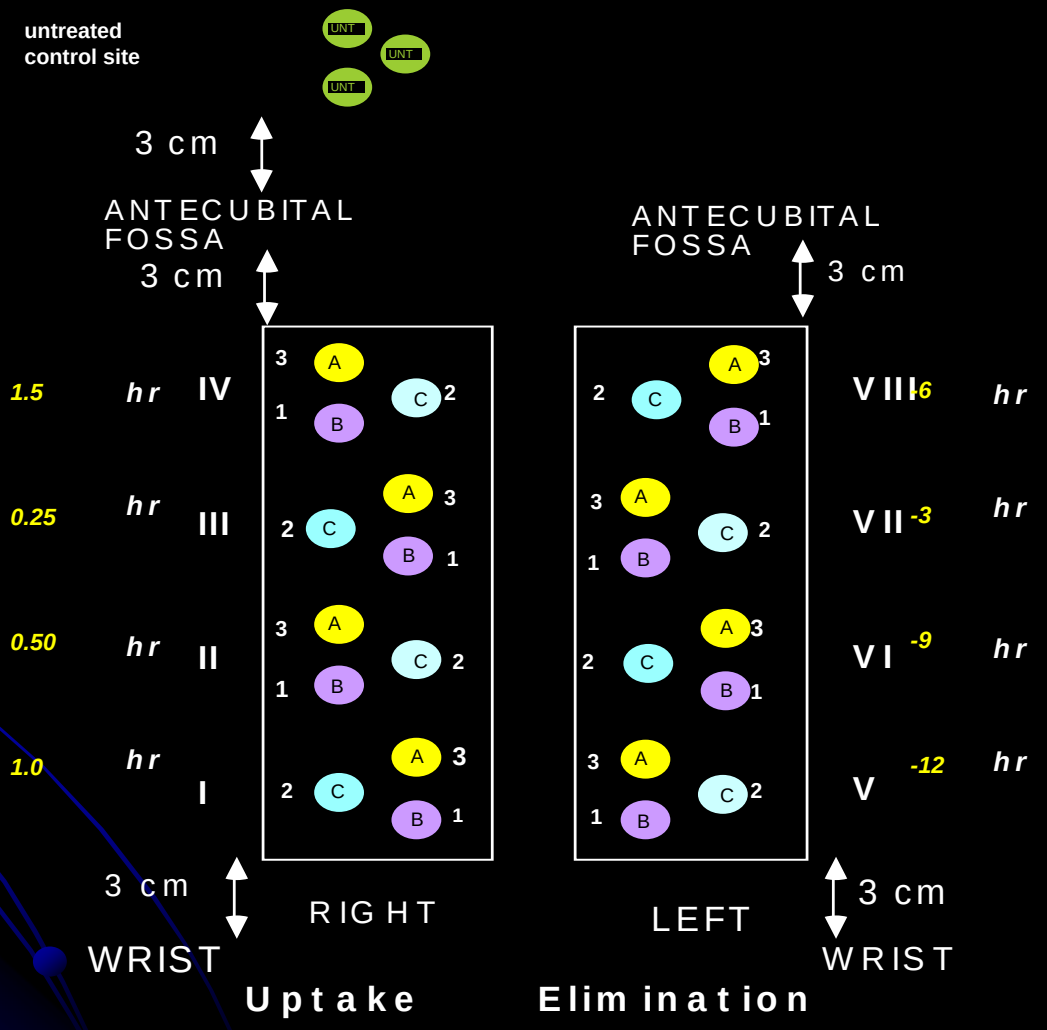
60 minutes prior to drug application	7 minutes prior to drug application
Wash forearms with gentle liquid soap Demarcate skin sites on forearms with prepared template	Tapestrip the designated untreated control skin sites



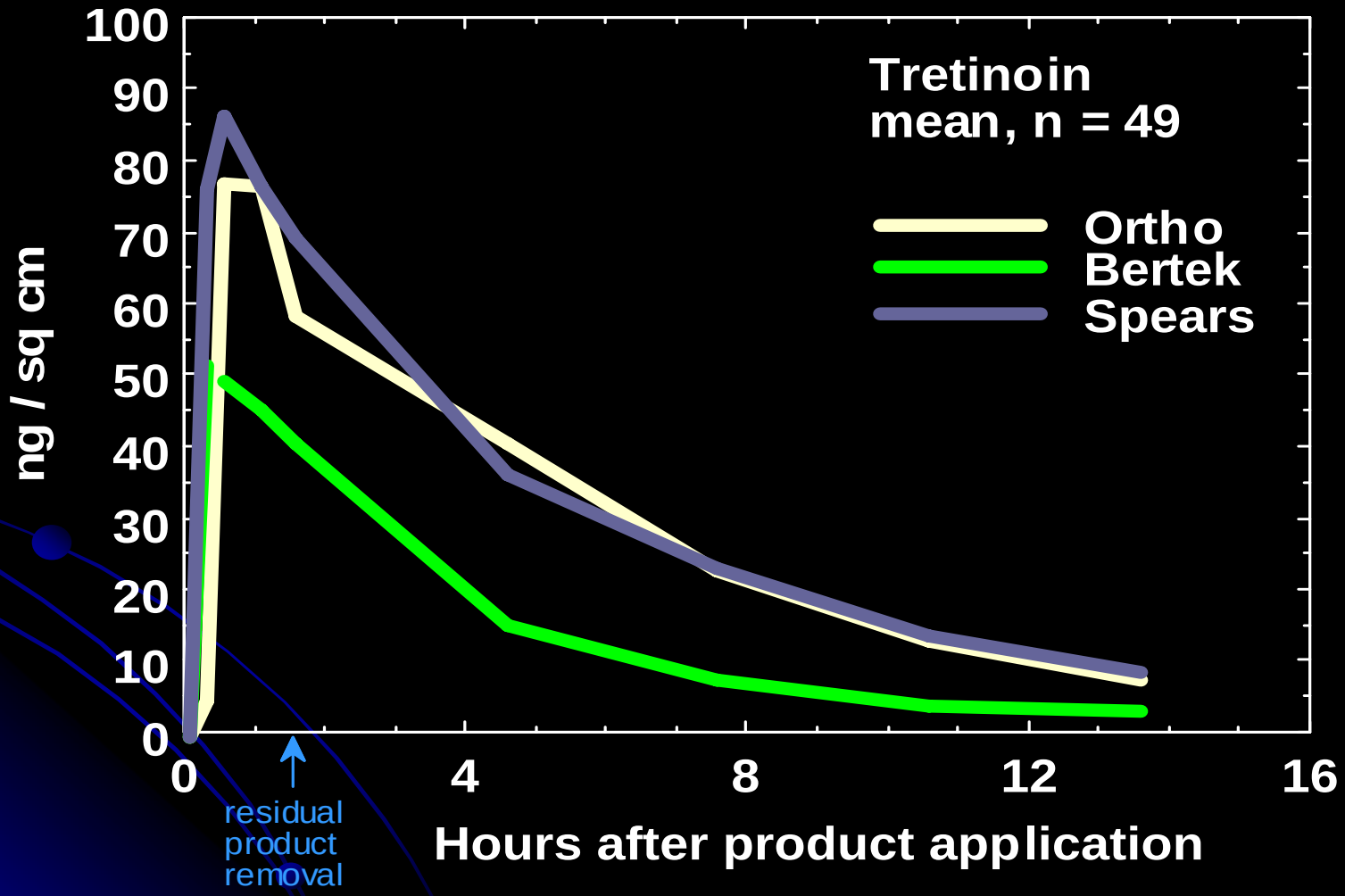
Key

*	Application time	0 hr (0830 on day 1)
↓	Drug Removal time	0.25, 0.50, 1.00 and 1.50 hours post drug application
↑	Tapestrippping collection times	1hr prior to drug application 0.25, 0.5, 1, 1.5, 4.5, 7.5, 10.5 and 13.5 hr after drug application

Product Application Randomization tretinoin gel, 0.025%



DPK Bioequivalence tretinoin gel, 0.025%

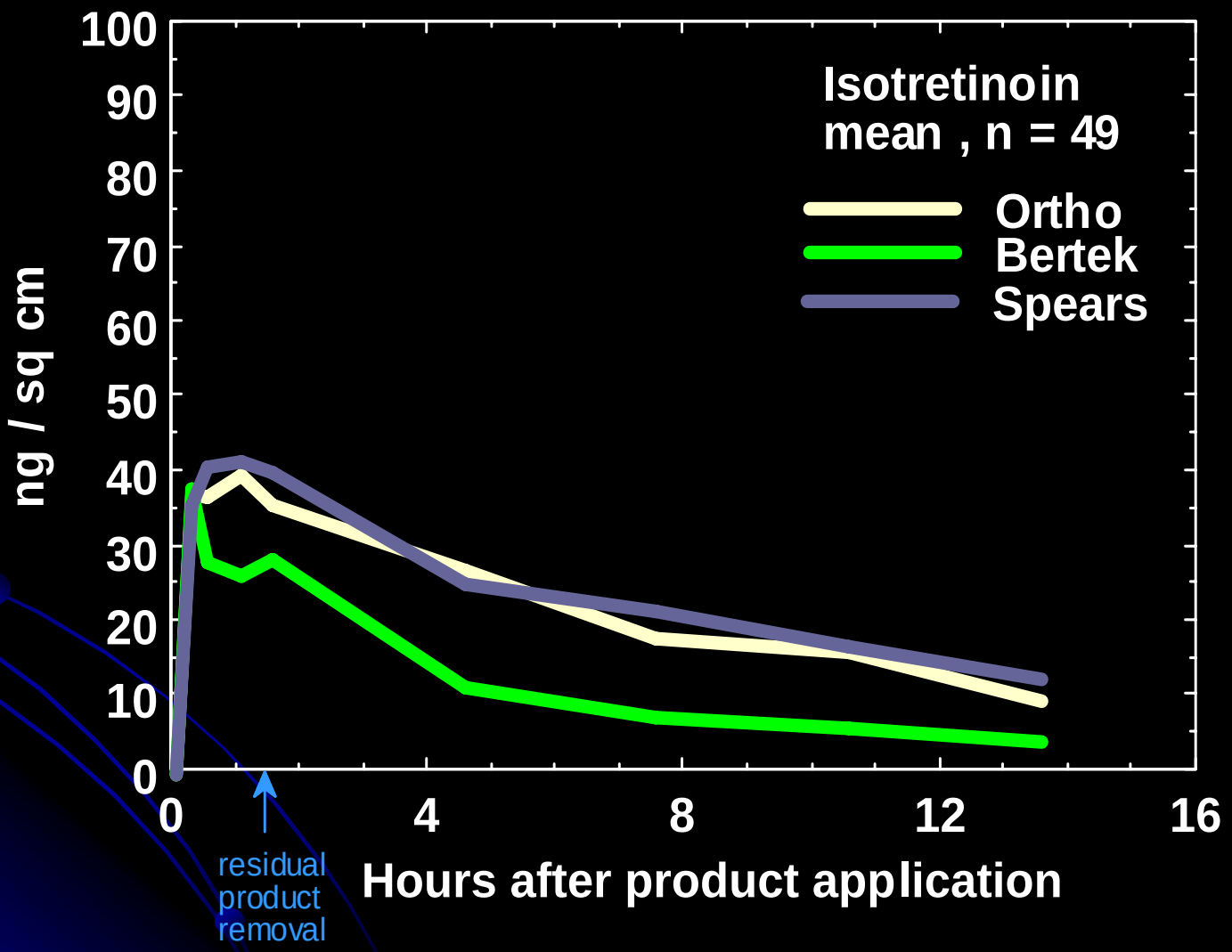


DPK Bioequivalence Tretinoin

Parameter	Bertek Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	68.394	105.335	67.6% ?83.9%	66.2% ?85.7%
AUC0-t	190.145	377.253	49.0% ?58.6%	48.1% - 59.6%

	Spear Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	110.955	105.335	94.0% - 116.7%	92.1% - 119.2%
AUC0-t	391.654	377.253	97.0% - 115.9%	95.3%- 118.0%

DPK Bioequivalence tretinoin gel, 0.025%

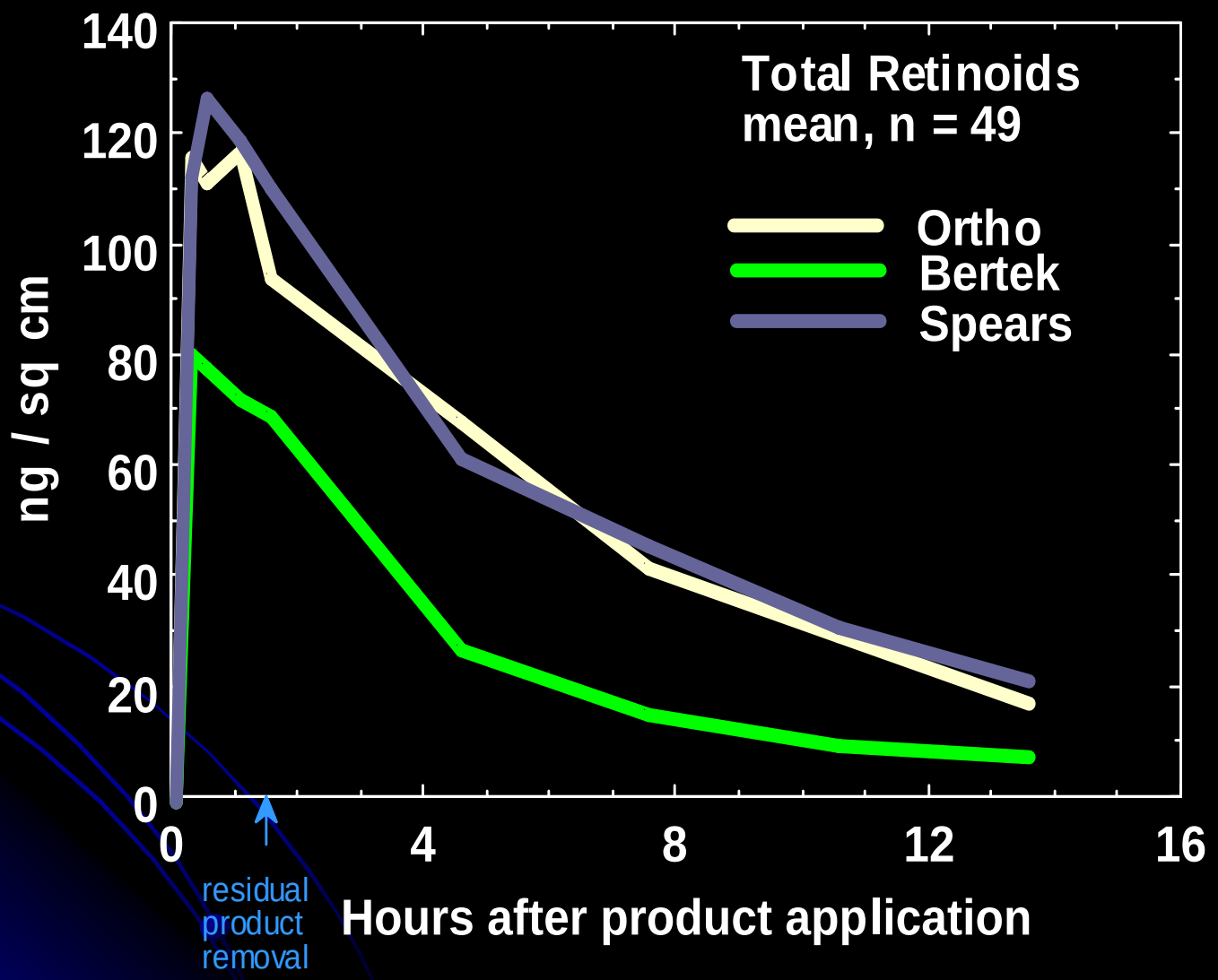


DPK Bioequivalence Isotretinoin

Parameter	Bertek Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	38.020	51.647	67.6% ?83.9%	66.2% ?85.7%
AUC0-t	149.210	282.096	49.0% ?58.6%	48.1% - 59.6%

	Spear Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	53.453	51.647	94.0% - 116.7%	92.1% - 119.2%
AUC0-t	294.124	282.096	97.0% - 115.9%	95.3%- 118.0%

DPK Bioequivalence tretinoin gel, 0.025%



DPK Bioequivalence Total Retinoids

Parameter	Bertek Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	106.117	155.414	61.3% ?77.8%	59.8% ?79.7%
AUC0-t	356.766	684.528	48.4% ?56.5%	47.6% - 57.4%

	Spear Test	Ortho Reference	Bioequivalence 90% CI	Bioinequivalence 95% CI
Cmax	165.450	155.414	94.6% - 120.2%	92.4% - 123.0%
AUC0-t	715.099	684.528	97.1% - 113.5%	95.6%- 115.2%

Bioequivalence Assessment of Three 0.025% tretinoin gel products

Method	Ortho vs. Spears Q1 Q2 similar	Ortho vs. Bertek Q1 Q2 different
DPK	BE	Not BE Ortho 2x > Bertek
Clinical Efficacy	BE	Not BE Ortho > Bertek
Clinical Safety	BE	Not BE Bertek 2x > Ortho

CONCLUSIONS

DPK Method for Bioequivalence Assessment 0.025% tretinoin gel

- DPK results predict Clinical Efficacy Results
- DPK provides mechanistic basis for Safety Results
- DPK is sensitive, reproducible and valid method for BE assessment

Innovator Incentives (Patents)

Innovator Incentives (Patents)

- Prior to 1984, a patent would run for 17 years from issue date or 20 years from filing
- W/H set to restore some incentive for innovation because pre-market approval requirements have increased
- W/H may restore up to 5 years not to exceed 14 years from the product's approval date

Innovator Incentives (cont.)

- URAA (June 8, 1995) made all patents in force or filed as of this date have the longer term of 17 years from issuance or 20 years from filing

- All patents filed after June 8, 1995 have an expiration date of 20 years from filing

Exclusivity Incentives

- NCE protection - 5 years
- New salt or ester - 3 years
- New use or dosage form - 3 years

Generic Incentives

- All approved products eligible for generic competition
- Eliminated requirement for duplicative clinical trials
- Created a regulatory process for faster approval of generic drugs

When can a Generic Drug be Marketed?

- After patent & exclusivity protection ends,
- patent owner waives its rights, or
- patent challenge is won, and
- FDA requirements are met

Patent Protection

- Applies to NDAs only
- Delays final approval of ANDAs
- Agency is concerned with drug substance, drug product and method of use patents
- Published in Orange Book

Patent Certifications

- Paragraph I - Patent not submitted to FDA
- Paragraph II - Patent already expired
- Paragraph III - Tentative approval
- Paragraph IV - Court involvement

Exclusivity Provisions

- Market protection
- 3 or 5 year period
- NCE prohibits ANDA submission
- Mutually exclusive
- 180 day exclusivity for first ANDA applicant(s) filed with a p IV certification to a particular patent/drug product

180 Day Exclusivity

- Blocks approval of subsequent ANDAs
- Awarded to first applicant(s) to file PIV to a listed patent/drug product, on the same day
- Triggered by either first commercial marketing or a court decision.
- Shared Exclusivity (multiple patents or multiple filers)

Tactics to delay Generic Competition

- Serial Patent Filings: multiple 30 month stays
- Agreements not to market: Generic and Innovator
- Agreements not to initiate litigation: Generic and Innovator
- Citizen's Petitions: change in BE studies, not same drug product…
- Changes to Reference Listed Drug Product.

Title XI of the Medicare Modernization Act

- Passed as law 12/8/2003
- Some provisions retroactive to August of 2003
- Only one 30 month stay per ANDA (some exceptions)
- Exclusivity based on drug product not by patent
- Provisions for Forfeiture of 180 day exclusivity

APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

20TH 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 MANAGEMENT
DIVISION OF DATABASE MANAGEMENT

2000

“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 their proposed products with

True and False Quiz

- 1. The Hatch-Waxman Amendment to the FD&C Act provided a mechanism for the approval of generic drug products.

  2. The Hatch-Waxman Amendments did not provide any benefits for innovator drug firms.

  3. Approval of an abbreviated new drug application requires review of large clinical studies assessing the effectiveness of the product.

  4. A generic drug may have a different route of administration than the reference drug.

  5. Facilities manufacturing generic drug products are not inspected by FDA.

True and False Quiz

- 6. The “Orange Book” contains therapeutic equivalence evaluations.

  7. Drug products that are rated “A” in the “Orange Book” may be substituted with full confidence.

  8. The “Orange Book” lists expiration dates for patents and exclusivities.

  9. To confirm bioequivalence, the rate and extent of absorption must not be statistically different when administered to humans at the same molar dose.

  10. Solution drug products must be tested with in vivo bioequivalence studies.

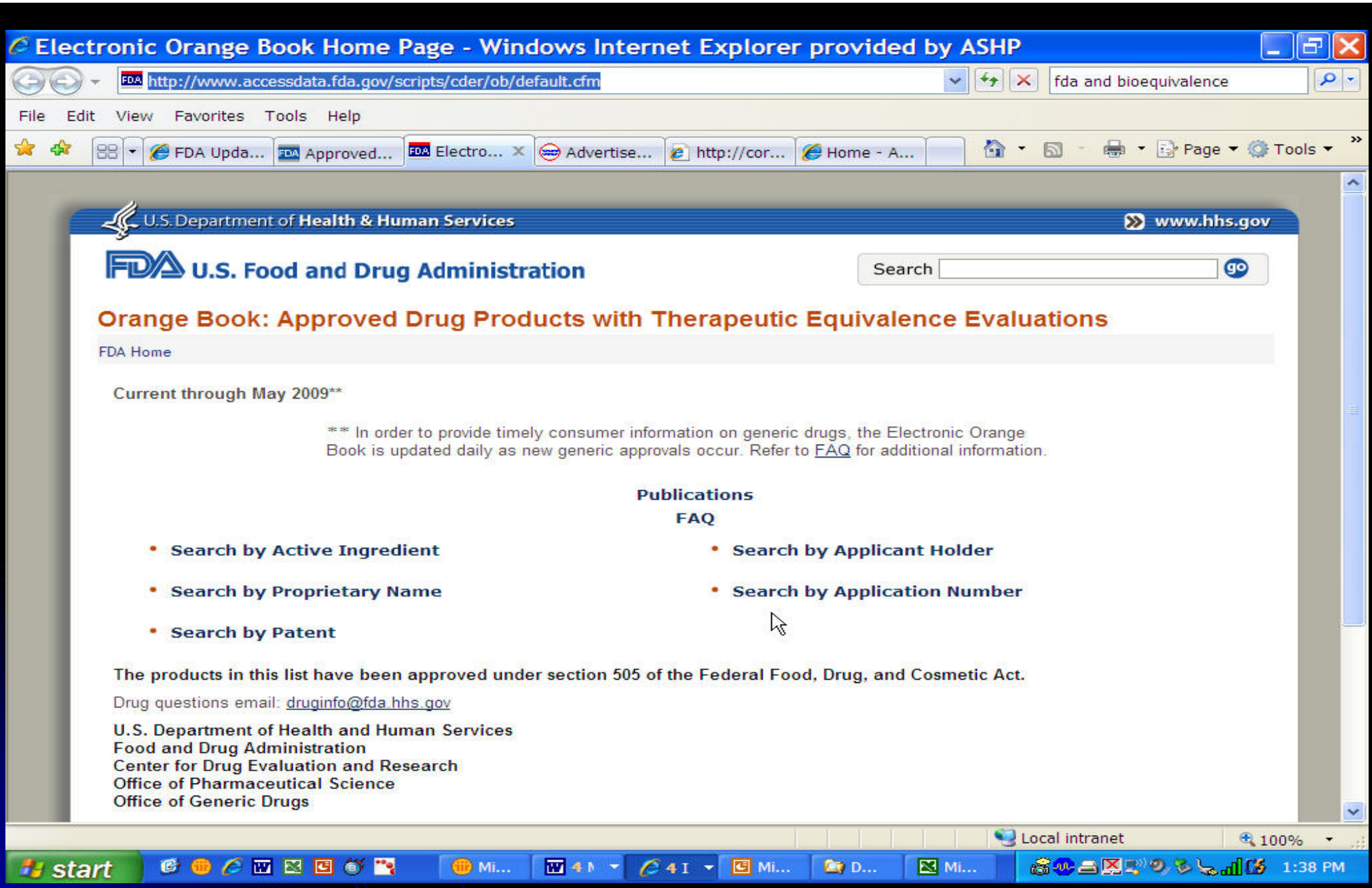
True and False Quiz

11. Statistical analysis of bioequivalence studies looks at the confidence intervals of the test/reference ratio.

12. There is only one way to determine bioequivalence.

13. Generic NTI drug products require different bioequivalence limits than other drug products.

- **ANSWERS:**
  - True
  - False
  - False
  - False
  - False
  - True
  - True
  - True
  - True
  - False
  - True
  - False
  - False



www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Narrow Therapeutic Range (NTI) Drugs

- Drug Products that are subject to therapeutic drug concentration or pharmacodynamic monitoring
  - Examples are: Digoxin, Lithium, Phenytoin, Warfarin
- Traditional bioequivalence limit of 80-125% is unchanged for these products

Narrow Therapeutic Ratio Drugs

- Less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) value

OR

- There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood

THEREFORE

- Safe and effective use of the drug products require careful titration and patient monitoring

Bioequivalence and Narrow Therapeutic Ratio Drugs

"FDA is prepared to use a more stringent criterion if differences of this size [e.g., the 90% confidence interval for the ratio of the test product mean AUC to that of the innovator must lie entirely within the interval (0.80-1.20) (now 0.80 to 1.25 on log transformed data)] are shown to be clinically significant." *No clinical data has been submitted to the Agency in the ten plus years since the hearing that would warrant the Agency narrowing the present confidence interval of 0.80 to 1.25 on any drug or class of drugs.* If a tighter statistical interval was used for NTI drugs, it is even possible that if an innovator firm reformulated its product, the product might not be bioequivalent to itself.

Challenges to Generic Substitution

- Legislation introduced in several states
  - NJ, TX, FL, AL, GA, and District of Columbia
- Anti-epilepsy and transplant medications, others
  - Adverse effects
  - Breakthrough seizures
  - Risk of organ rejection
- Mandate that pharmacists inform patient and provider of the following substitutions:
  - Brand-to-brand
  - Generic-to-generic
  - Brand-to-generic

Are generic drugs a bad bargain? - TODAY Health - Windows Internet Explorer provided by ASHP

http://today.msnbc.msn.com/id/30940044

bmission of bioequivalence data

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Are generic drugs a bad bargain?

All of us want cheaper medicine — but not if it costs us our health

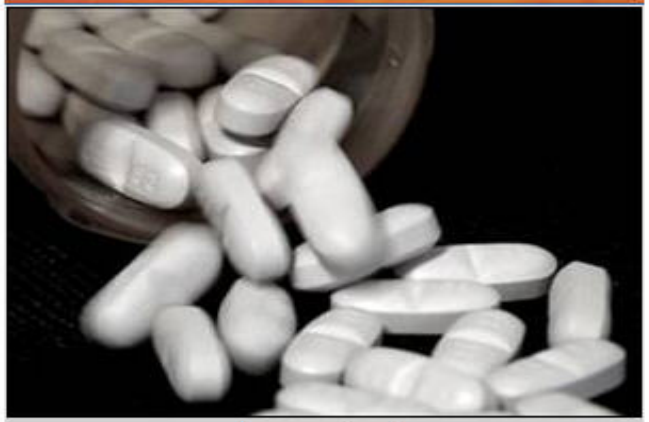
By Katherine Eban
SELF
updated 8:50 a.m. ET, Tues., May 26, 2009

Just when Beth Hubbard should have been feeling great, her health fell apart.

A 34-year-old housewares designer in the St. Louis area, Hubbard had recently gotten married. She liked the creativity of her career. And she'd conquered her mild **depression** and fatigue with a combination of exercise, rest and medicine, including the antidepressant Wellbutrin XL. But in the fall of 2006, shortly after she refilled her prescription — her pharmacy giving her this time Budeprion XL, a generic version of the drug — her good health gave way.

Within a month, she had gained 15 pounds, couldn't sleep well, developed gastrointestinal problems and felt such extreme fatigue and lack of motivation that she thought about quitting her job. She cried and called in sick for days at

Video



Launch

How safe are generic drugs?
May 26: According to the Congressional Budget Office, generic drugs save consumers at least $8 billion every year, but are they always the best choice? NBC's chief medical editor Dr. Nancy Snyderman reports on the risks and benefits associated with generics.
Today show

More from SELF.com

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ASHP Activities

- Participation in Generic Carve-Out Coalition
  - Monitor and respond to legislation
  - Resources for expert testimony
  - Local and national media outreach
- ASHP Government Affairs Division
  - State legislative conference call
- ASHP Public Relations
  - Media outreach

ASHP Policy on Generic Substitution of Narrow Therapeutic Index Drugs

- To support the current processes used by the Food and Drug Administration (FDA) to determine bioequivalence of generic drug products, including those with a narrow therapeutic index, and to recognize the authority of the FDA to decide if additional studies are necessary to determine equivalence; further,
- To oppose a blanket restriction on generic substitution for any medication or medication class without evidence from well-designed, independent studies that demonstrate inferior efficacy or safety of the generic drug

Generics

- Generally speaking, therapeutic or diagnostic products consisting of, or derived from, living organisms.
- Statutorily speaking (PHSA):

"*a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product,… applicable to the prevention, treatment, or cure of a disease or condition of human beings.*"

Why Are “Biogenerics” So Controversial?

- “Biologics” are a rapidly growing segment of medical care in the U.S.
- The cost to develop and manufacture biologics is substantially higher than for traditional “small molecule” drugs.
- Prices to patients are accordingly also very high.

Why Are “Biogenerics” So Controversial?

- There is no regulatory pathway for the approval of “generic” biologics.
- Thus, even after patents expire, there is little prospect for competition from lower-cost alternatives.
- There also is no mechanism for challenging biologics patents in advance of marketing a potentially infringing product.
- Current generic drug laws inadequately protect innovators, who do not want to replicate that system for biologics

Why Are “Biogenerics” So Controversial?

- The generic drug approval statute (“Hatch-Waxman”) specifically applies only to versions of innovative drugs approved under section 505(b) of the FDCA;
- Biologics are approved under the PHSA, a separate statute from the FDCA.
- However, there are some “biologics” approved under FDCA for which generic approval may be possible.
- Highly complex molecules are difficult to characterize and produce

生物药分类系统（BCS）

- BCS 是一种科学框架，它能够根据药物的水溶性和肠内渗透性对其进行分类。

生物药分类	溶解性	渗透性
I	高	高
II	低	高
III	高	低
IV	低	低

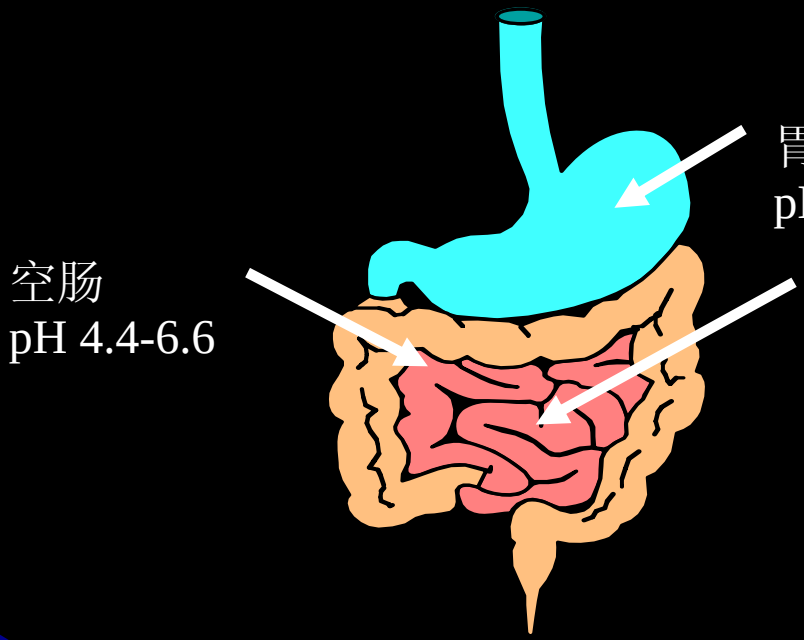
生物药分类系统

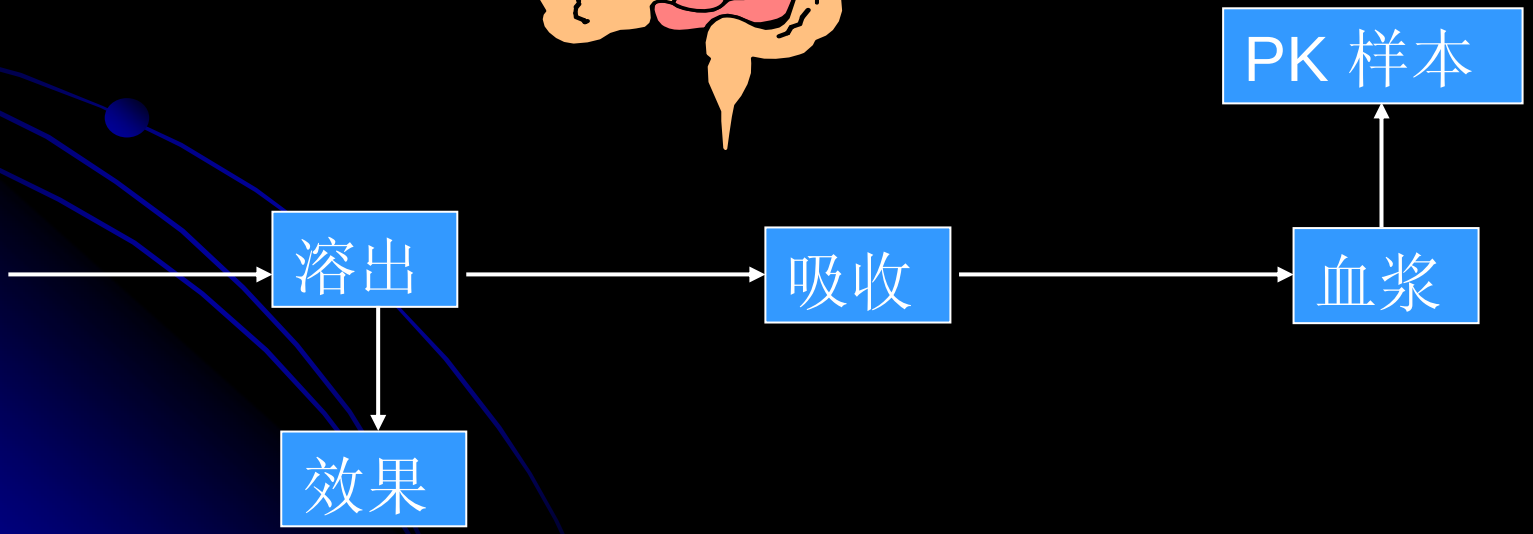
- 溶解性
  - *高溶解度* 37ºC时，药物的最大剂量能够溶解在250 mL或更少的pH值介于1至7.5之间的水溶液中
- 渗透性
  - *高渗透性* 药物在人体的肠内吸收程度达到或高于90%
- 溶出率
  - *快速溶出* 在0.1mol/L HCl溶液，pH值为4.5的缓冲溶液，以及pH值为6.8的缓冲溶液中，30分钟内药物标识量的85% 或以上完全溶出

基于生物药分类系统的生物等效性研究的豁免

- 适用于那些在特定条件下，能够表现出*较快的*(30分钟内达到85%)并与获准参比药物*相似的*溶出率的固体口服测试药物，同时它们还需满足以下条件：
  - 这些产品是**药学等效的**
  - 原料药具有**高溶解度、高渗透性** 并且不是**治疗范围狭窄** 的药物
  - 使用的辅料不会影响药物吸收

肠胃用药的生物等效性





技术文件的格式要求

1. 首页函	
2. FDA 1571表	
3. 内容目录	21 CFR 312.23(a)(2)
4. 介绍性陈述/总研究计划	21 CFR 312.23(a)(3)
5. 研究者手册	21 CFR 312.23(a)(5)
6. 研究方案	21 CFR 312.23(a)(6)
7. CMC信息	21 CFR 312.23(a)(7)
8. 药理/毒理学资料	21 CFR 312.23(a)(8)
9. 先前人用经验	21 CFR 312.23(a)(9)
10. 附加信息	21 CFR 312.23(a)(10)

常用的网址

- Office of Generic Drug Website
  - http://www.fda.gov/cder/ogd/index.htm
- Individual Product Bioequivalence Recommendations
  - http://www.fda.gov/cder/guidance/bioequivalence/default.htm
- Dissolution Methods for Drug Products
  - http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
- Model Bioequivalence Data Summary Tables
  - http://www.fda.gov/cder/ogd/index.htm#bioequivalence
- Inactive Ingredient Database
  - http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
- FDA Guidance Page
  - http://www.fda.gov/cder/guidance/guidance.htm#Biopharmaceutics