

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: November 26, 2002
To: Dockets Management Branch (HFA-305)
From: Lafayette Gross
Office of Generic Drugs
Subject: The FDA Process for Approving Generic Drugs

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: The FDA Process for Approving Generic Drugs
Presented for: Blue Cross Blue Shield of Michigan
Continuing Medic/Pharmacy Association
Date Presented: October 29, 2002
Presented by: Gary Buehler, R.Ph, Director
Number of Pages: 9



Attachment

90S-0308

M 729

Blue Cross Blue Shield
of Michigan
Continuing
Medical/Pharmacy
Education Program



The FDA Process for Approving Generic Drugs

Gary J. Buehler, R.Ph
Director

October 29, 2002

Did you know that generic drugs...

- Are safe and effective alternatives to brand name prescriptions
- Can help both consumers and the government reduce the cost of prescription drugs
- Are currently used in 44% of all prescriptions dispensed

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And...

- Save an average of \$45.50 for every prescription sold
- Currently save consumers \$56.7 billion/year
- Can save consumers an additional \$1.32 billion/year for every 1% increase in the use of generic drugs

Source: National Association of Pharmaceutical Manufacturers, December 15, 2000

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Hatch-Waxman Amendments to FFD&C Act - 1984

- Considered one of the most successful pieces of legislation ever passed
- Created the generic drug industry
- Increased availability of generics
 - 1984 12% prescriptions were generic
 - 2000 44% prescriptions were generic - yet only 8% of revenue for prescription drugs
- Compromise legislation to benefit both brand and generic firms

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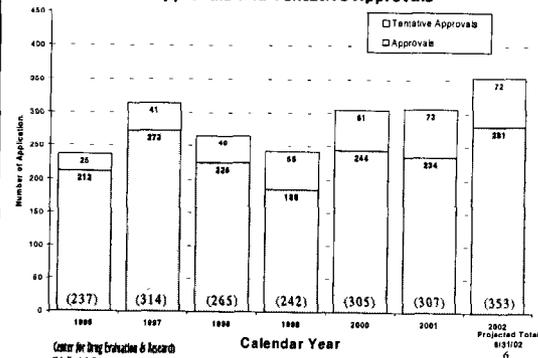
Hatch-Waxman Amendments to FFD&C Act - 1984

- Allowed generic firms to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities (do not have to repeat expensive clinical and pre-clinical trials)
- Allowed patent extensions and exclusivities to innovator firms

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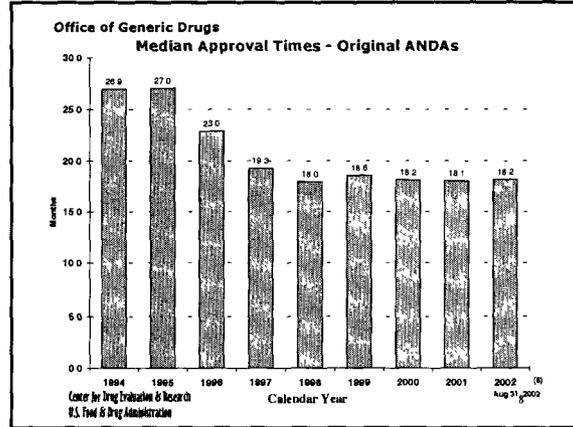
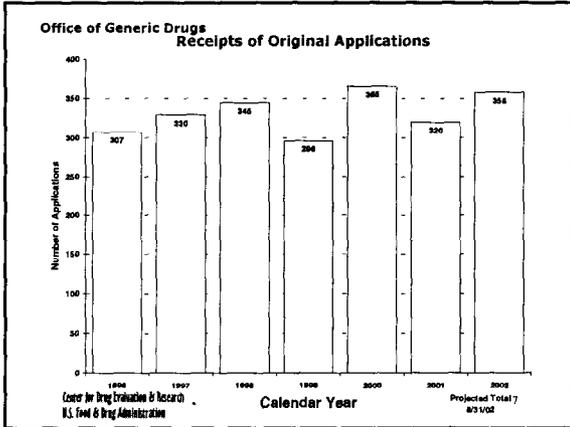
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Office of Generic Drugs Approvals and Tentative Approvals



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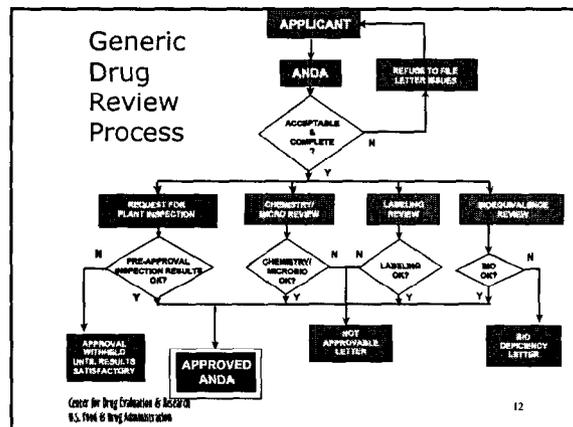
NDA vs. ANDA Review Process

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	6. Bioequivalence
7. Clinical Studies	
8. Bioavailability	

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- What are the requirements for a generic drug?**
- Labeling
 - Chemistry/Microbiology
 - Bioequivalence
 - Legal
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- How do we assure the quality of generic drugs?**
- First 5 steps of review process are identical to NDA process
 - Bioequivalence for complicated products is discussed with the same staff that reviewed the brand product
 - FDA has experience with the product
 - Scientific literature published
 - Product is known to be safe
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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)

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

Examples of Information Covered in a Chemistry Review

- Qualitative and quantitative listing of all active and inactive ingredients; including grade of each component

Examples of Information Covered in a Chemistry Review

- Review of manufacturing and controls includes evaluation of:
 - Process for manufacturing
 - Controls (Inspections, sample points, test, methods, acceptance criteria) in place from the receipt of the raw material to the labeling and storage of the finished product; includes the Certificate of Authorization (COA) from the raw material manufacturer and the firm's own testing and specifications in a COA
 - Synthesis of the active pharmaceutical ingredient(s) (API) (raw material, drug substance) or authorization to reference a Drug Master File (DMF)

Examples of Information Covered in a Chemistry Review

- Impurity profile of the API
- Stability of the API
- Characterization of degradation products with drug substance and drug product
- Microbiological testing when appropriate (Reviewed by Microbiologists)

Examples of Information Covered in a Chemistry Review

- Batch formulation and batch records
 - Manufacturing record provides a representation of the formula, manufacturing instructions, description and size of manufacturing equipment



Examples of Information Covered in a Chemistry Review

- Description of the manufacturing facilities in general; identification of all firms and facilities involved
- Stability profile (with information on such things as container/closure system); adequacy of protocol and methods
- Evaluation of methods validation information prior to laboratory evaluation

Examples of Information Covered in a Chemistry Review

- Container/Closure Systems
- Environmental Assessment compliance

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

**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

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FOOD AND DRUG ADMINISTRATION
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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

B-Rated Drugs

- Exist because of the evolution of FFD & C Act
 - FFD & C Act 1938 - safety only
 - 1962 Amendments - Added effectiveness requirement
 - DESI program to assess efficacy of drugs approved between 1938 and 1962
 - 1970 - Regulation initiating the ANDA procedure

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B-Rated Drugs

- 1977 - Bioavailability/Bioequivalence (BA/BE) regulations finalized
 - Required BA data in NDAs; BE data in ANDAs
 - Divided DESI effective drugs - products that needed BE shown in vivo and in vitro (bio problem drugs) and products that BE may be shown in vitro only (non-bio problem drugs)
- Many bio problem drugs approved as safe and effective before 1977 - in vivo determination of BE deferred for reasons such as inadequate methodology
- FDA determined BA/BE regulations could not be used retrospectively

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B-Rated Drugs

- 1984 Hatch-Waxman - gave FDA statutory authority to require a demonstration of BE before an ANDA could be approved. No longer allowed approval of bio problem drugs
- Products for which in vivo demonstration of BE was deferred are listed as therapeutic inequivalent or "B" rated
- Those still appearing in the Orange Book are about 3% - FDA does not have data demonstrating equivalence or inequivalence

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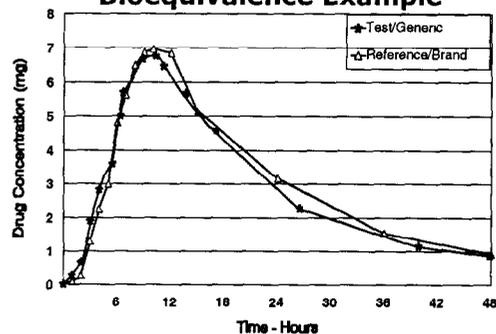
Definition of Bioequivalence

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

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Bioequivalence Example



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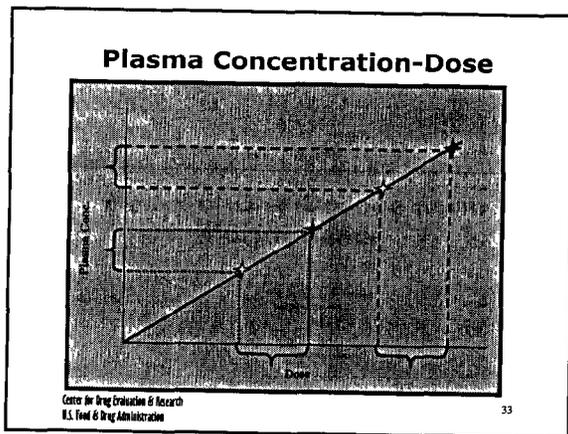
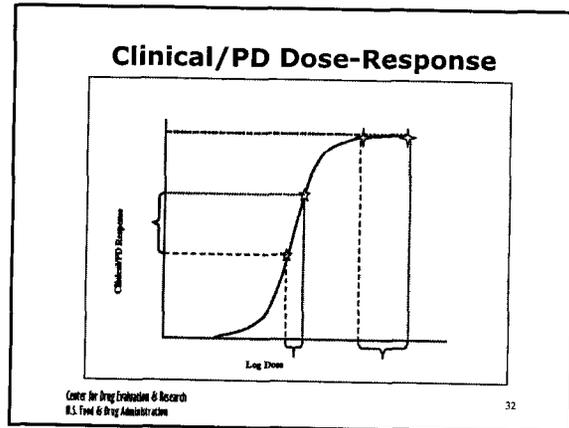
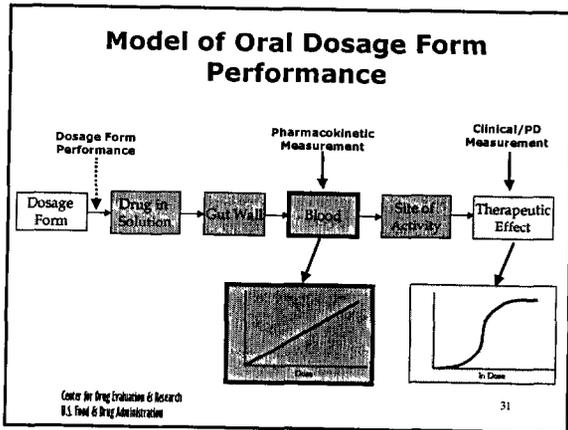
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Purpose of BE

- 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

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- ### Approaches to Determining Bioequivalence (21 CFR 320.24)
- In vivo measurement of active moiety or moieties in biologic fluid
 - In vivo pharmacodynamic comparison → FeV₁, Albuterol
Blanching Study
Topical Corticosteroid
 - In vivo limited clinical comparison → Topicals
Nasal Suspensions
 - In vitro comparison → Questran - Binding Studies
Nasal Solutions-Sprayer
Evaluation
Propofol - Droplet Size
 - Any other approach deemed appropriate by FDA
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- ### Study Designs
- Single-dose, two-way crossover, fasted
 - Single-dose, two-way crossover, fed
 - Alternatives
 - Single-dose, parallel, fasted Long Half-Life (wash-out)
Amiodarone, Etidronate
 - Single-dose, replicate design Highly Variable Drugs
 - Multiple-dose, two-way crossover, fasted Less Sensitive
Clozapine (Patient Trials)
Chemotherapy Trials
 - Clinical endpoint study Topicals
Nasal Suspensions
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- ### 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
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Statistical Analysis (Two One-sided Tests Procedure)

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

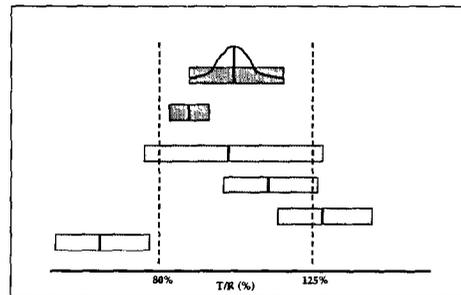
Statistical Analysis 80 - 125 %

- 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% ($\alpha = 0.05$ significance level)
 - T/R = 80/100 = 80%
 - R/T = 80% (all data expressed as T/R so this becomes 100/80 = 125%)

Possible BE Results (90% CI)

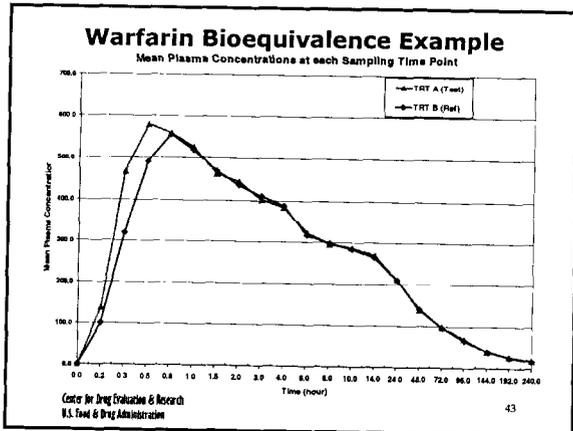


Narrow Therapeutic Range (NTI) Drugs

- 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

Generic Warfarin 10mg Tablets

	AUC _{0-∞}		AUC _{0-∞}		Cmax	
	PI	CI	PI	CI	PI	CI
Applicant #1	1.02	(98-105)	0.98	(95-100)	1.02	(95.1-110)
Applicant #2	1.00	(97-102)	1.00	(97.4-102.4)	0.99	(90-100)
Applicant #3	0.99	(96-102)	1.03	(100.4-105.7)	0.94	(89-99)



- ### In Vivo Bioequivalence Inspections
- Covers clinical and analytical components
 - Objectives
 - Verify quality and integrity of the scientific data
 - Ensure rights and welfare of human subjects are protected
 - Ensure compliance with the regulations and promptly follow-up on significant problems (research misconduct; fraud)
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- ### Generic Drug Education Program
- Congress acknowledged overall need for educational program
 - FY'02 \$400,000 allocation
 - Program to educate the public on the quality of generic drug products
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- ### Physician Focus Group Findings
- MDs know little about FDA review and approval process--especially how it differs for generic products
 - Lack of knowledge and understanding of bioequivalence (sameness) evaluation testing
 - "Placebo" effect - product looks different
 - Need more information
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- ### Getting the Message Out
- Target health care providers (Physicians, Pharmacists) as well as consumers
 - Continuing Education (CE) Programs
 - Office of Training and Communications (OTCOM) Specialists in CDER
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- ### Educational Program Activities
- | | |
|------------------------|-------------------|
| Print PSA | Focus Testing |
| Brochures | NAPs Article |
| Posters | Give-Aways |
| Web Site Consumer Page | Bus/Train Ads |
| Magazine Ads | Movie Theater Ads |
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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. Call 1-888-INFO-FDA or visit our website at www.fda.gov/cder/ to learn more. **Generic Drugs: Safe, Effective, FDA Approved.**

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You know that question
that goes through your mind
when you take your
generic drug?
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If you're experiencing
anxiety about taking your
generic drug,
read this ad and repeat
as needed.

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**Generic Drug Education Program
Posters**

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www.fda.gov/cder/consumerinfo/DPAdefault.htm

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