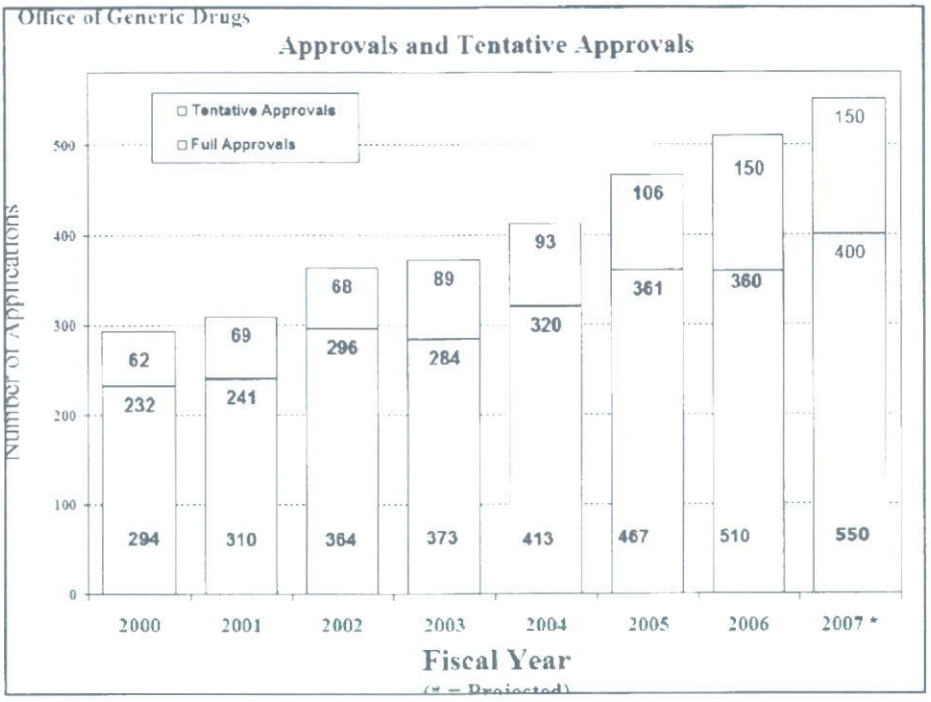
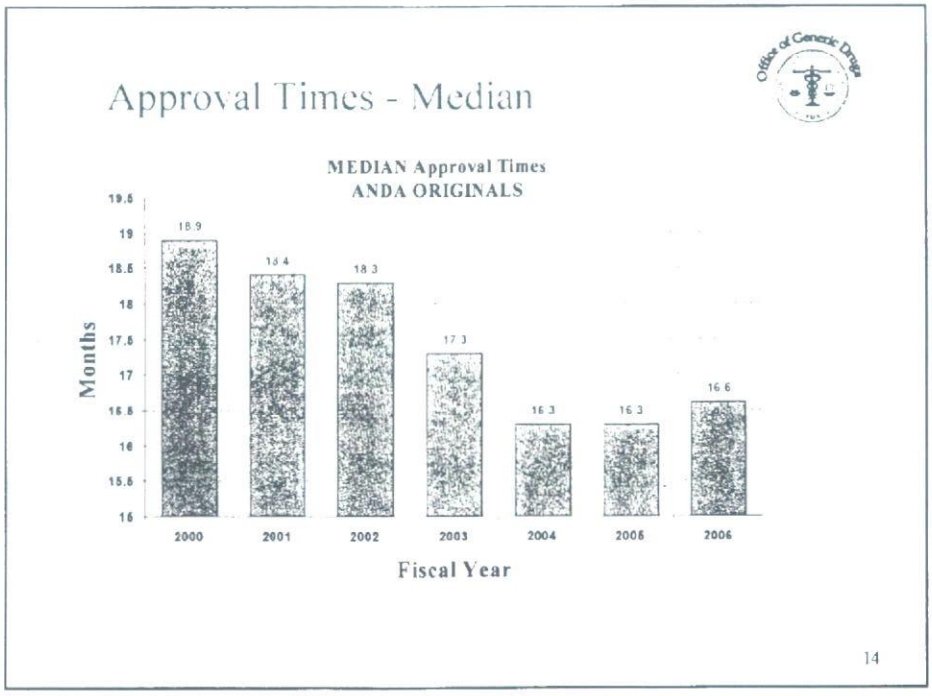
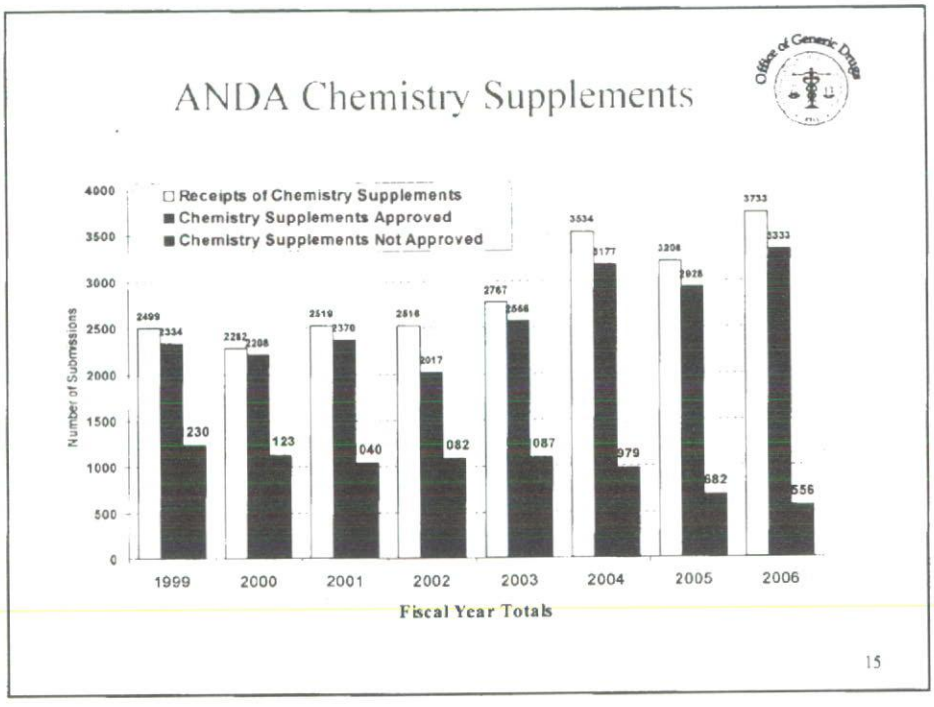
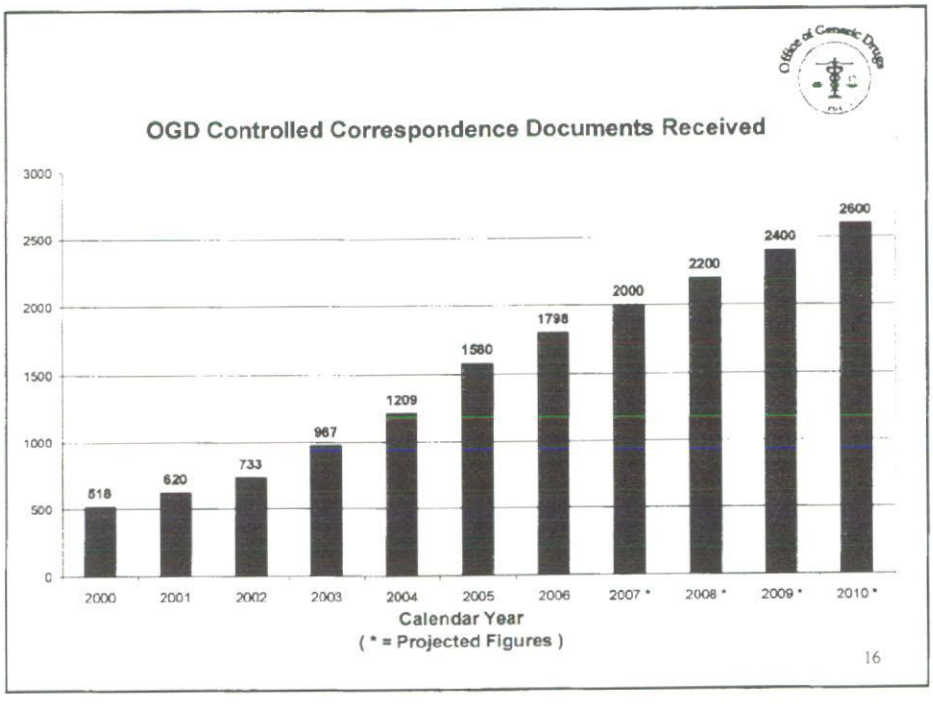
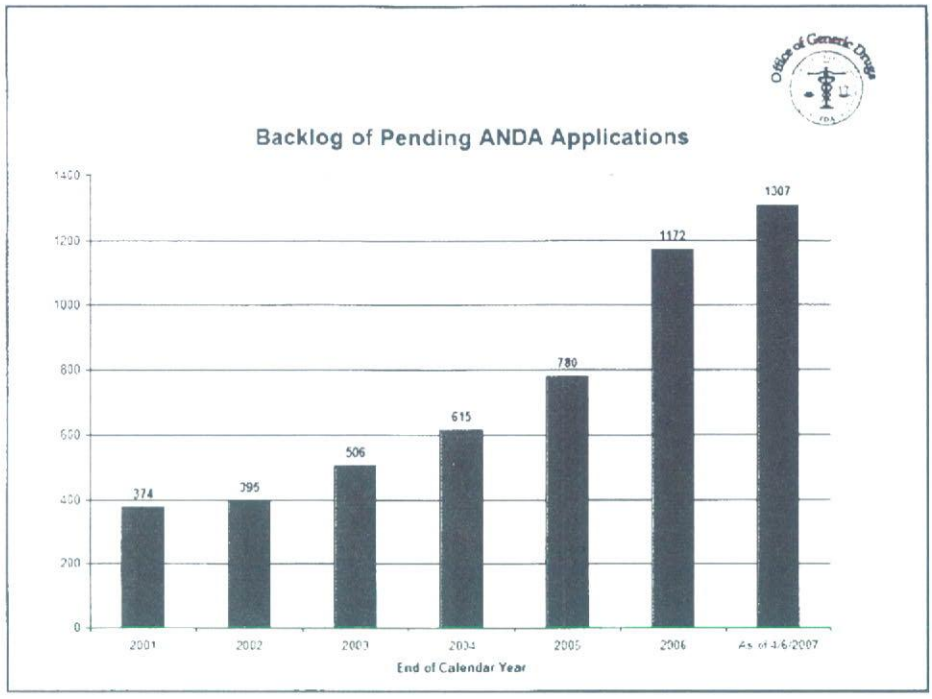

Office of Generic Drugs
Approvals and Tentative Approvals
Tentative Approvals
Full Approvals
Number of Applications
0
100
200
300
400
500
62
232
294
69
241
310
68
296
364
89
284
373
93
320
413
106
361
467
150
360
510
150
400
550
2000
2001
2002
2003
2004
2005
2006
2007 *
Fiscal Year


Approval Times - Median
Office of Generic Drugs
MEDIAN Approval Times
ANDA ORIGINALS
Months
15.5
16
16.5
17
17.5
18
18.5
19
19.5
18.9
18.4
18.3
17.3
16.3
16.3
16.6
2000
2001
2002
2003
2004
2005
2006
Fiscal Year
14


ANDA Chemistry Supplements
Office of Generic Drugs
Receipts of Chemistry Supplements
Chemistry Supplements Approved
Chemistry Supplements Not Approved
Number of Submissions
4000
3500
3000
2500
2000
1500
1000
500
0
2499
2334
230
2282
2208
123
2519
2370
040
2816
2017
082
2767
2566
087
3534
3177
979
3208
2928
882
3733
3333
556
1999
2000
2001
2002
2003
2004
2005
2006
Fiscal Year Totals
15


Office of Generic Drugs
OGD Controlled Correspondence Documents Received
3000
2500
2000
1500
1000
500
0
518
620
733
967
1209
1580
1798
2000
2200
2400
2600
2000
2001
2002
2003
2004
2005
2006
2007 *
2008 *
2009 *
2010 *
Calendar Year
(* = Projected Figures)
16



Important First Generic Approvals – 2007

- FENTANYL TRANSDERMAL SYSTEM, 12 MCG/HOUR (Duragesic-12)
- PROPRANOLOL HCL EXTENDED-RELEASE CAPSULES (Inderal LA)
- DEXMETHYLPHENIDATE HCL TABLETS (Focalin)
- VALACYCLOVIR HCL TABLETS (Valtrex)
- SERTRALINE HCL TABLETS (Zoloft)
- RABEPRAZOLE SODIUM DELAYED-RELEASE TABLETS (Aciphex)
- RANITIDINE ORAL SOLUTION USP (Zantac Syrup)
- CITALOPRAM HBR CAPSULES (Celexa)
- MOEXIPRIL HCL AND HYDROCHLOROTHIAZIDE TABLETS (Uniretic)
- DIDANOSINE FOR ORAL SOLUTION (PEDIATRIC POWDER), (Videx)
- PREDNICARBATE OINTMENT (Dermatop)
- CIPROFLOXACIN EXTENDED-RELEASE TABLETS (Ciprox XR)
- NADOLOL AND BENDROFLUMETHIAZIDE TABLETS USP, (Corzide)
- CEFIXIME FOR ORAL SUSPENSION USP (Cefixime)
- NIMODIPINE CAPSULES (Nimotop)
- ZOLPIDEM TARTRATE TABLETS (Ambien)
- PRAVASTATIN SODIUM TABLETS (Pravachol)
- METOPROLOL SUCCINATE EXTENDED-RELEASE TABLETS USP (Toprol XL)
- PAROXETINE HCL EXTENDED-RELEASE TABLETS (Paxil CR)

18

NDA vs. ANDA Review Process

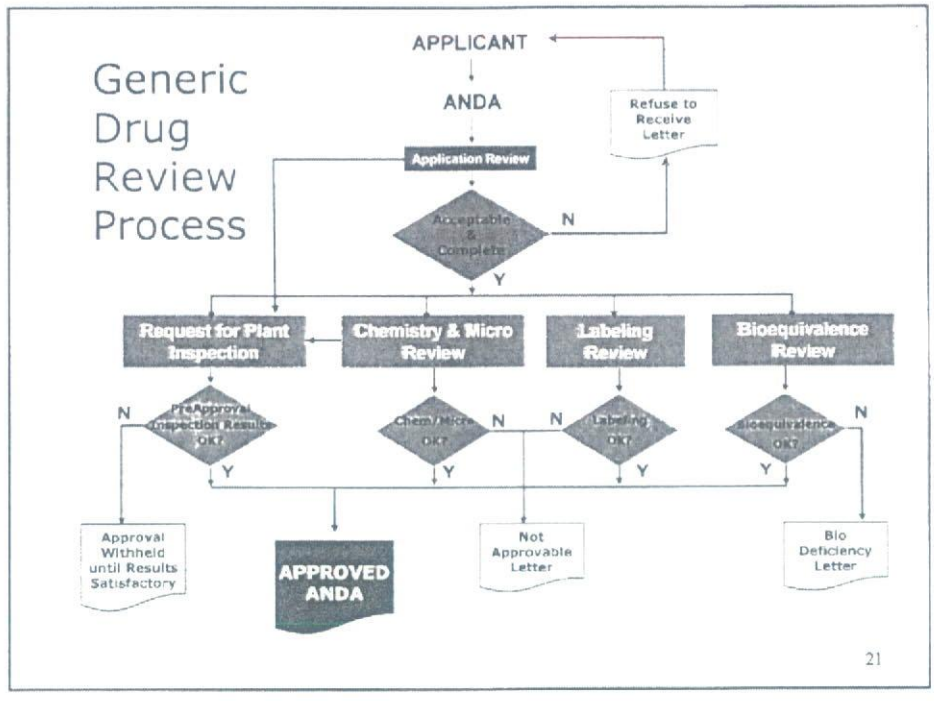
Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies 7. Clinical Studies 8. Bioavailability	6. Bioequivalence

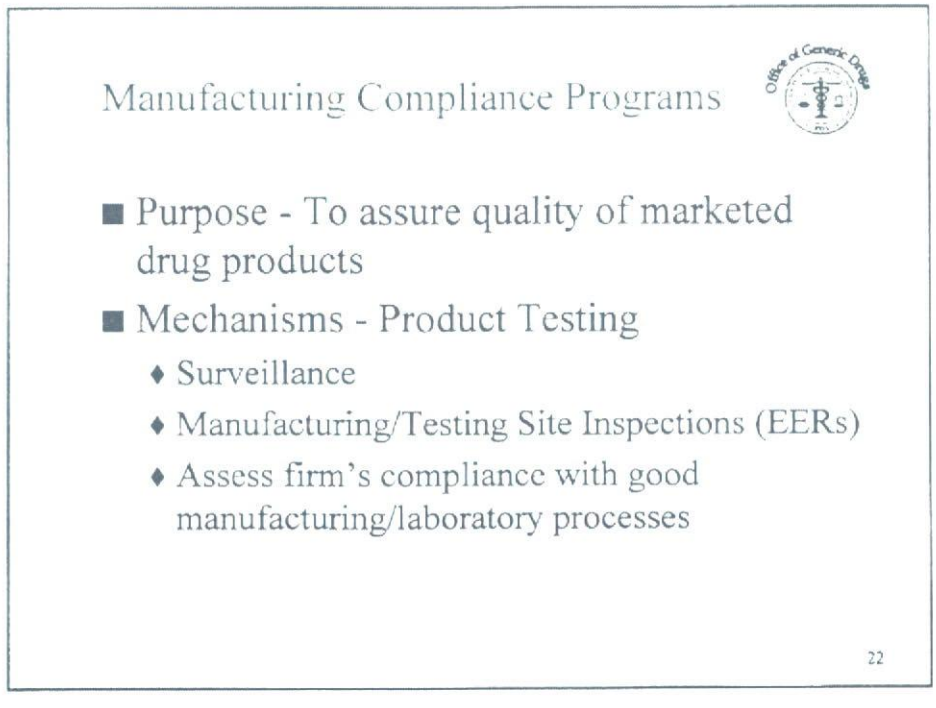
19

NDA vs. ANDA Review Process

- NDA Review = Lower volume (ave. 25 approvals/year), but Higher Complexity (Pre-Clinical, Clinical Trials, etc.)
- ANDA Review = Higher volume (425 approvals/year), but Lower Complexity (Safety & Efficacy already established)

20


Generic Drug Review Process
APPLICANT
ANDA
Refuse to Receive Letter
Application Review
Acceptable & Complete?
N
Y
Request for Plant Inspection
Chemistry & Micro Review
Labeling Review
Bioequivalence Review
N
Pre-Approval Inspection Results OK?
Y
Chem/Micro OK?
N
Y
N
Labeling OK?
Y
N
Bioequivalence OK?
Y
Approval Withheld until Results Satisfactory
APPROVED ANDA
Not Approvable Letter
Bio Deficiency Letter
21


Manufacturing Compliance Programs
Office of Generic Drugs
■ Purpose - To assure quality of marketed drug products
■ Mechanisms - Product Testing
♦ Surveillance
♦ Manufacturing/Testing Site Inspections (EERs)
♦ Assess firm's compliance with good manufacturing/laboratory processes
22

Chemistry Review

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

23

Labeling Review

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

24

Definition of Bioequivalence (BE)

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

25

Purpose of BE Review

- 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

26

Clinical Review Staff

- Dr. Dena Hixon, M.D.
- Reviews bioequivalence studies with clinical endpoints
- Evaluates safety issues (inactive ingredients, adverse events, etc.)
- Assesses clinical issues in ANDAs (effect of different vehicles, inactive ingredients)
- Assesses equivalence challenges

27

OGD Project Manager Role

- Discipline specific PMs
- Review process based on **First-In = First-Reviewed** – Not PDUFA
- Chemistry review drives the review process; hence, Chemistry PM monitors overall review progress
  - Ex: Informs Bioequivalence/Microbiology PM of need for reviews
  - Prepares full approval package

28

OGD Project Manager Role

- Bioequivalence PM
  - Controlled correspondence
  - Bioequivalence waiver requests
  - Bioequivalence review queues
- Microbiology PM
  - Monitors review queue
  - Assures ANDAs needing microbiology review are identified

29

OGD Project Manager Role

- All fulfill other traditional PM functions, e.g., communication with industry, assuring all actions are documented

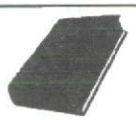
30

Research Initiatives by OGD Scientific Staff
Lawrence Yu, Ph.D., Director for Science

- Respond to Scientific Challenges
- Develop Bioequivalence Methods
  - MDIs
  - Topicals
  - Injectable Suspensions
- Expand In-House Capabilities
- Work with Office Testing & Research in developing/hiring expertise
- External Contracts

31

"Orange Book Staff"



- "Approved Drug Products with Therapeutic Equivalence Evaluations"
- 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

32

OGD Education Committee

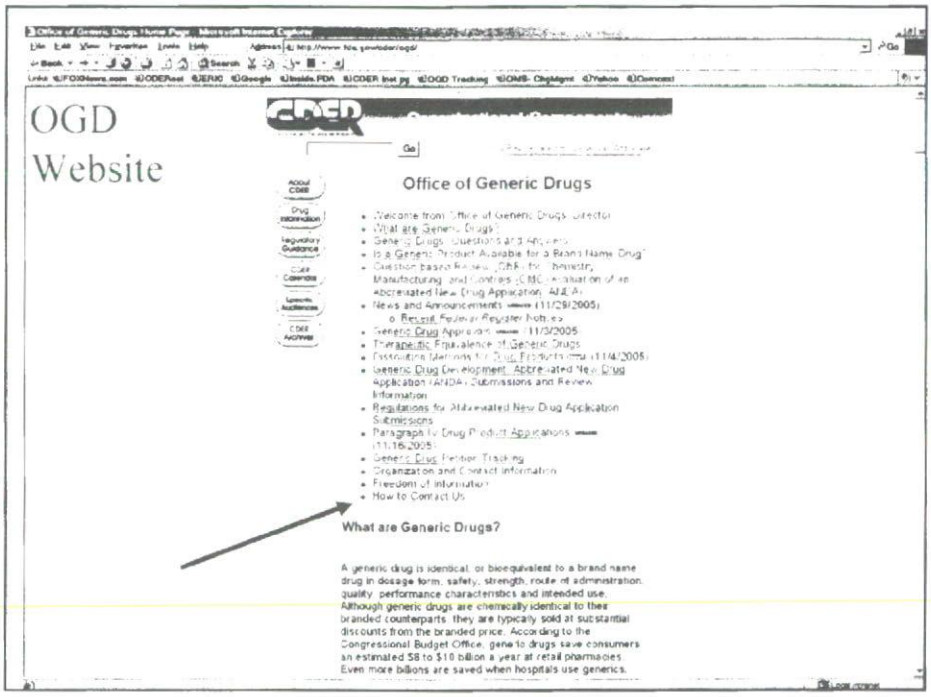
- Purpose – To provide educational offerings for the OGD staff including training and plant visits
- Committee has at least one member from each OGD review discipline
- Plant trips
- OGD Reviewer Forum
- Workshops – Open to others on space available basis

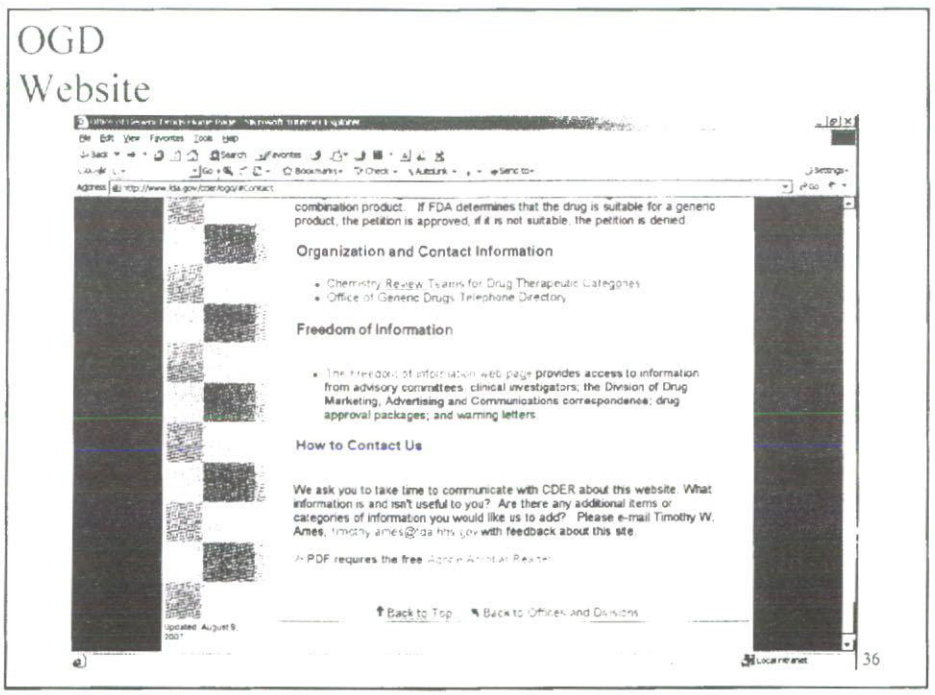
33

New Drug Review Divisions Interactions with OGD

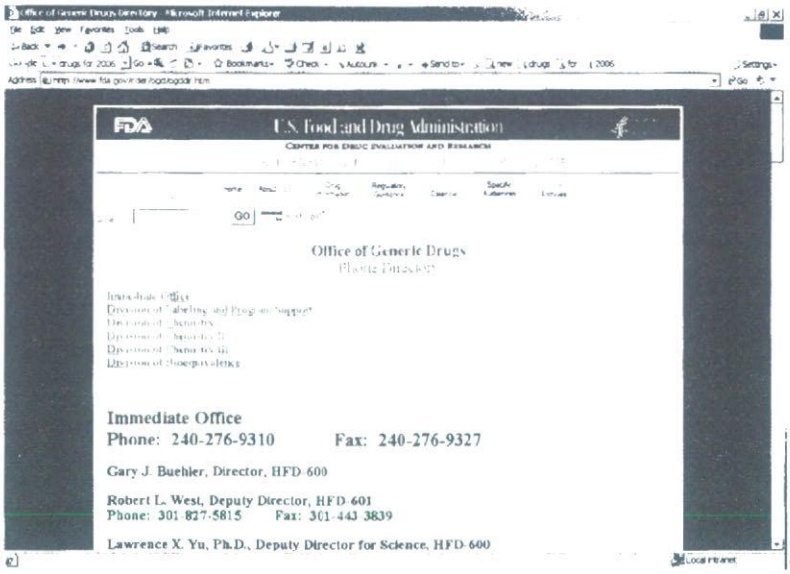
- Bundled Reviews
- Consults
- Risk Management/Educational Programs
- Labeling Supplements
- Best Pharmaceuticals for Children Act (BPCA)
- OGD Website – Contact list

34

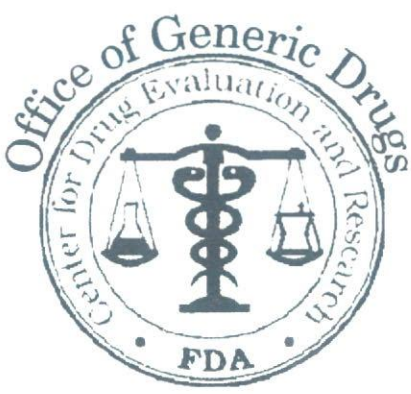

OGD
Website
CDER
Office of Generic Drugs
What are Generic Drugs?
A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.
Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics.


OGD
Website
combination product. If FDA determines that the drug is suitable for a generic product, the petition is approved; if it is not suitable, the petition is denied.
Organization and Contact Information
Chemistry Review Teams for Drug Therapeutic Categories
Office of Generic Drugs Telephone Directory
Freedom of Information
provides access to information from advisory committees; clinical investigators; the Division of Drug Marketing, Advertising and Communications correspondence; drug approval packages; and warning letters.
How to Contact Us
We ask you to take time to communicate with CDER about this website. What information is and isn't useful to you? Are there any additional items or categories of information you would like us to add? Please e-mail Timothy W. Ames, timothy.ames@fda.hhs.gov with feedback about this site.
Back to Top
Back to Offices and Divisions
36

OGD
Website



37



7500 Standish Place (HFD-600)
Rockville, MD 20855
240-276-9310

38

Impact of USP Monographs
on the
Office of Generic Drugs

Review Process

October 1, 2007

Frank O. Holcombe, Jr., Ph.D.
Associate Director for Chemistry
Office of Generic Drugs

USP/NF

United States Pharmacopeial Convention

- **Promote Public Health Through Authoritative Standards and Information**
- **United States Pharmacopeia and National Formulary**
- **Independent**
- **Public Process**
- **Non-Governmental**

United States Pharmacopeia & National Formulary

The Official Compendia of Standards

Organization

- **General Notices**
- **Official Monographs**
- **General Chapters**

- **National Formulary**

USP/NF

Monographs

- **Official Articles**
  - **Drug Substance**
  - **Inactive Ingredient (excipients)**
  - **Drug Product**

- **Official drug products/devices**
  - **Ingredients meet Compendial Monographs**

USP/NF

Monograph

Drug Substance Parameter Examples

- * Description
- * Packaging and Storage
- * Reference Standards (as available)
- * Identification
- Residue on Ignition
- Heavy Metals
- Organic Volatile Impurities
- Chromatographic Purity
- Water/Loss on Drying
- * Assay

USP/NF

Monograph

Drug Product Parameter Examples

- * Description
- * Packaging and Storage
- * Reference Standards (as available)
- * Identification
- pH
- Dissolution
- * Uniformity of Dosage Units
- Related Compounds
- Water/Loss on Drying
- * Assay

USP/NF

Food Drug and Cosmetic Act

Section 201 (g)(1) - "drug" means

- **(A) articles recognized in the official United States Pharmacopeia, ... National Formulary....**
- **(D)articles intended for use as a component of any articles specified in (A)....**

Section 501(b) - Adulterated Drugs

- **Strength, Quality, Purity**

Section 502(e), (g) - Misbranded Drugs

- **Established Name; Packaging**

USP/NF

Title 21 - Code of Federal Regulations

Section 314.50(d)(1) - Chemistry, manufacturing, and controls

- **Drug Product, Drug Substance -**
  - **Reference to ... U.S. Pharmacopeia ... may satisfy relevant requirements of this paragraph.**

Section 314.50(e) - Samples and labeling

- **Reference standards recognized ... official compendium ...**

USP/NF

Monograph

Concern - **Identity**
- **Quality**
- **Strength**
- **Purity**

Provides - **Tests**
- **Methods**
- **Acceptance Criteria**

USP/NF					
Monograph			**Application Review Goals**		
Concerns	-	**Identity**	**Concerns**	-	**Identity**
	-	**Quality**		-	**Quality**
	-	**Strength**		-	**Strength**
	-	**Purity**		-	**Purity**
				-	**Bioequivalence**
Provides	-	**Tests**	**Evaluate**	-	**Tests**
	-	**Methods**		-	**Methods**
	-	**Acceptance Criteria**		-	**Acceptance Criteria**

USP/NF

Application Review Goals

Additional Concerns

- **Manufacturing**
- **Development**
- **Scale Up**
- **Non-USP materials**
- **Non-USP attributes**

USP/NF

Review Process

- **Monograph**
  - ***Required* Criteria**
  - **Provides Defined Methods**
  - **Provides Basis for Standard Procedures**
  - **Provides Structure for Generalized Acceptance Criteria**
  - **A *Partial* Basis for Specification Setting**

USP/NF

Review Process Issues

- **Monograph • A *Partial* Basis for Specification Setting**
  - **Criteria are Official**
  - **Defined for Release and Shelf Life**
    - **Stability Indicating Methods?**
  - **Criteria are Generally Process-specific**
  - **Single source vs Multi-source**
    - **Impurities/Degradants**
    - **Substitution**
  - **Multiple Methods**

USP/NF

Monograph at Time of Application Approval

Year	Drug Substance	Drug Product	Distinct DS (% total app)
1997	60 %	35 %	44 %
1998	59 %	57 %	53 %
1999	80 %	61 %	58 %
2000	75 %	62 %	68 %
2004*	-----	48%	-----

*January - June