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Generic Drugs – Application and Regulatory Review

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Outline

- Compare and contrast between the generic drugs and new drugs
- Generic drug application filing and regulatory review
- Achievements and challenges in the regulatory review for generic drug applications
- Career opportunities in generic drug regulatory review

New Drug Application (NDA)

- NDA is submitted based on FD&C Act 505(b).
- NDAs are submitted for:
  - New molecular entity
  - New formulation of previously approved drug
  - New combination of two or more drugs
  - New indication (claim) for already marketed drug

Abbreviated New Drug Application (ANDA)

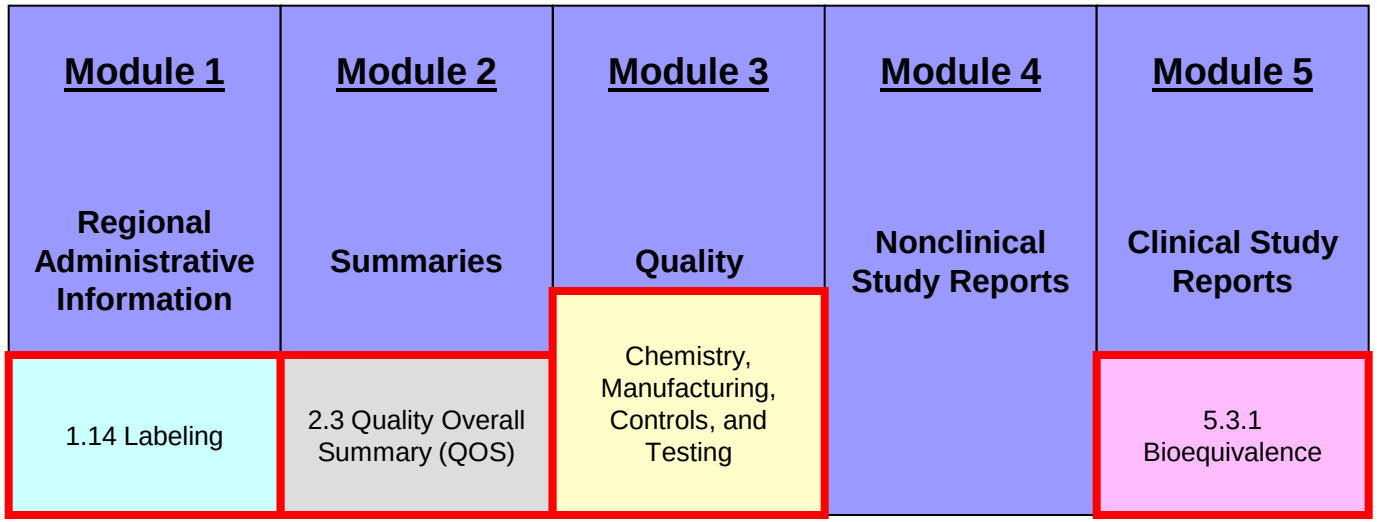
- ANDA is submitted based on FD&C Act 505(j).
- ANDAs are submitted for:
  - Generic drugs; a NDA must be previously approved and listed, known as the reference listed drug (RLD)

Note: ANDA may not be submitted for five years after the date of the approval of the New Molecular Entity (NME).

Requirements for NDA *vs.* ANDA

NDA	ANDA
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Testing	3. Testing
4. Labeling	4. Labeling
5. Inspections	5. Inspections
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Submission for NDA *vs.* ANDA



ICH M4: Common Technical Document for the Registration

CTD Submission Format Example

Based on the ICH M4Q: The CTD – Quality, the follow drug substance information should be included:

- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

Patent and Exclusivity

- **Patents** are granted by the *Patent and Trademark Office* anywhere along the development lifeline of a drug and can encompass a wide range of claims.
  - Patents expire 20 years from the date of filing. Many other factors can affect the duration of a patent.
- **Exclusivity** is exclusive marketing rights granted by the *FDA* upon approval of a drug and can run concurrently with a patent or not.
  - Orphan Drug (ODE) - 7 years
  - New Chemical (NCE) - 5 years
  - Pediatric Exclusivity (PED) - 6 months added
  - "Other" Exclusivity - 3 years for a "change" if criteria are met
  - *Patent Challenge (PC) - 180 days (this exclusivity is for ANDAs only)*

Patent for NDA *vs.* ANDA

NDA

- Patent information is required to be submitted with all new drug applications at the time of submission of the NDA.
- FDA relies on the NDA applicant or patent owner's signed declaration stating that the patent covers an approved drug product's formulation, composition or use.

ANDA

- A certification for each patent listed in the "Orange Book" for the RLD must state one of the following:

  (I) No Patent Filed

  (II) Patent Has Expired

  (III) Patent Will Expire

  (IV) Patent Challenge

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Review Process for NDA *vs.* ANDA

NDA

- Lower volume (average 25 approvals/year)
- Higher complexity (pre-clinical and/or clinical trials, etc.)
- One drug one application
- Pre-submission face-to-face meetings (IND phases)
- User fee (PDUFA) from 1992

ANDA

- Higher volume (more than 500 approvals/year)
- Lower complexity (safety and efficacy already established)
- One drug multiple applications
- User fee (GDUFA) from 2013

User Fee Rates for NDA vs. ANDA

	FY 2013		FY 2014	
	NDA (PDUFA)	**ANDA (GDUFA)**	**NDA (PDUFA)**	**ANDA (GDUFA)**
Total Fee for FY	$718,669,000	$299,000,000	$757,028,000	$305,659,000
New Application	$1,958,800 (with clinical data)	$51,520	$2,169,100 (with clinical data)	$63,860
	$979,400 (without clinical data)		$1,084,550 (without clinical data)	
Supplement	$979,400 (with clinical data)	$25,760 (PAS only)	$1,084,550 (with clinical data)	$31,930 (PAS only)
Type II DMF	---	$21,340	---	$31,460
Facility (Domestic/ Foreign)	$526,500	$175,389 / $190,389 (FDF)	$554,600	$220,152 / $235,152 (FDF)
		$26,485 / $41,458 (API)		$34,515 / $49,515 (API)
Product	$98,380	---	$104,060	---
Backlog	---	$17,434	---	---

Note: The rates are based on Federal Register Vol.77 No.207 (10/25/2012) and Vol.78 No.149 (8/2/2013).

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Requirement for ANDAs

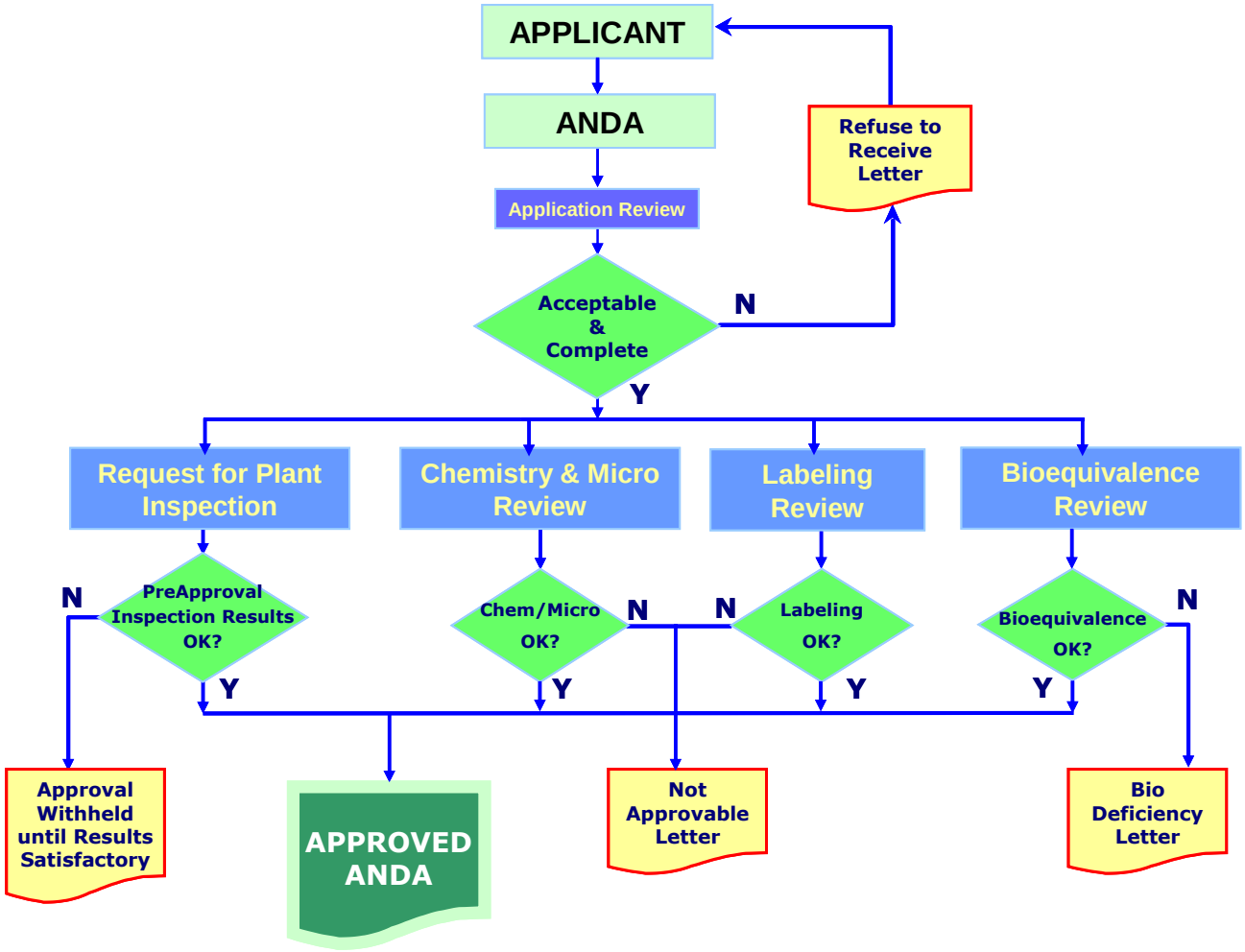
- Must have an approved reference product (RLD) and a patent certification
- Must be *Therapeutic Equivalent* to a reference product
- Meet the quality standards for chemistry and/or microbiology
- All related facilities have acceptable cGMP compliance

Therapeutic Equivalence

Therapeutic Equivalence includes:

- Pharmaceutically Equivalent (PE)
  - Same active ingredient(s)
  - Same dosage form
  - Same route of administration
  - Identical in strength or concentration
  - May differ in characteristics such as shape, excipients, packaging...
- Bioequivalent (BE)
  - Two drugs demonstrate same rate and extent when they become available at the site of drug action

Generic Drug Review Process



Filing Review

- Filing review is conducted to determine whether the application is sufficiently complete to permit a substantive review.
- Acceptance/Refuse to Receive (RTR) letter is issued based on completeness of the ANDA.
- Updating the regulatory filing checklist on a quarterly basis (calendar year) and on an as needed basis.

Filing checklist: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf

Bioequivalence Review

- Evaluate bioequivalence study acceptability
  - Clinical portion (subject treatment)
  - Analytical portion (biological fluid analysis)
  - Statistical portion (are products bioequivalent?)
- Select appropriate in vitro dissolution method (solid dosage forms only)
  - Stability and controls testing
- Grant biowaivers where appropriate
- Review bioequivalence protocols

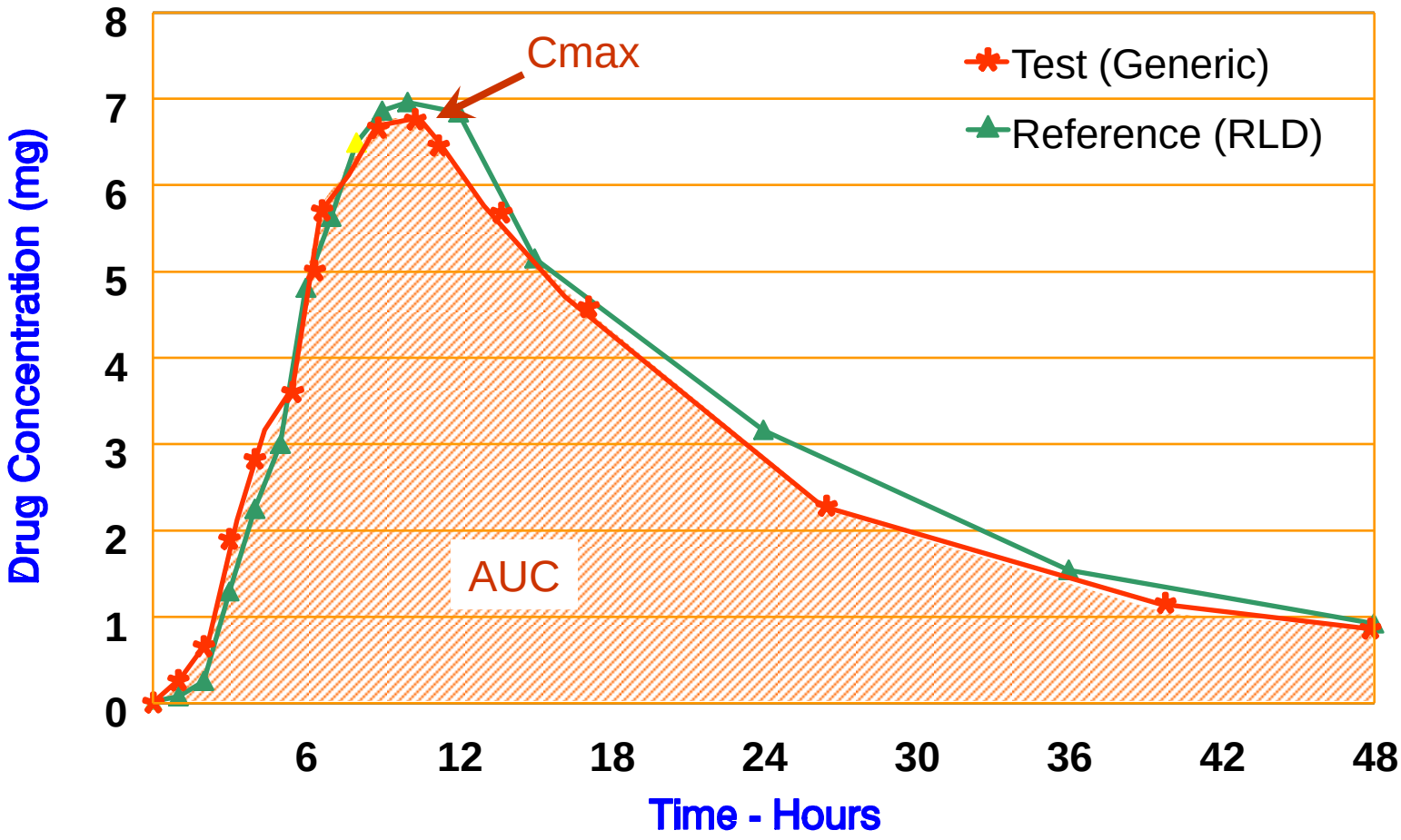
Bioequivalence Protocols: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

Bioequivalence

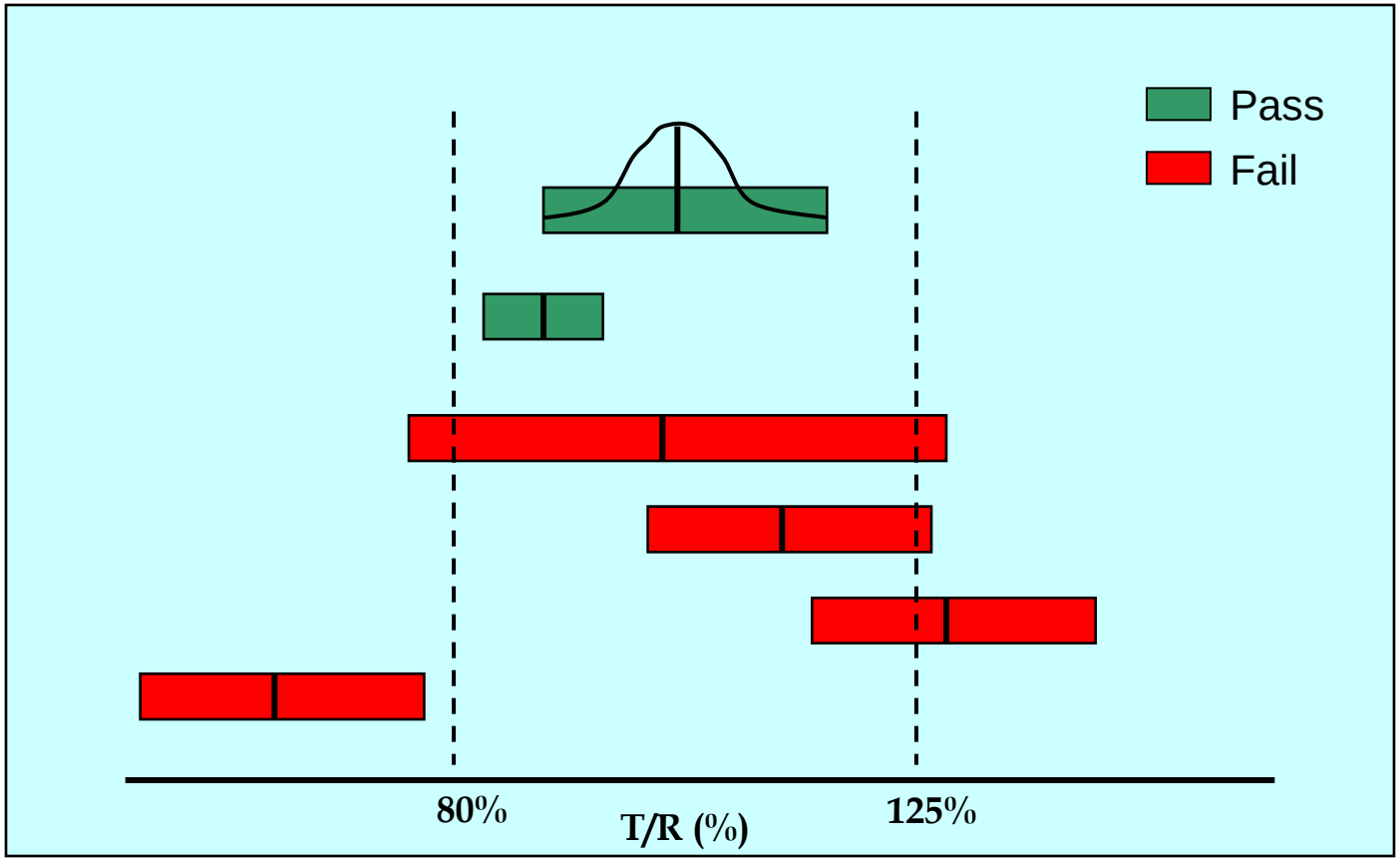
- Generic products is compared, in studies to the reference listed drug (RLD)
- Most studies compare the blood levels of the active moiety or moieties
- The generic product must be equivalent within certain pre-specified limits:

AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80%-125%

Bioequivalence Example



Possible BE Results (90% CI)



Biowaivers

21 CFR Part 320 provides situations where *in vivo* bioequivalence studies can be waived:

- Solutions (parenteral, oral, *etc.*)
- Drug Efficacy Study Implementation (DESI)
- Biopharmaceutics Classification System (BCS)
- Usually lower strengths of a product line

Labeling Review

- Reviews for “Same” as brand name labeling (with exceptions)
  - Labeling text to reflect differences in excipients, specific pharmacokinetic data
  - How supplied information - packaging container
  - Pharmacy practice issues - to prevent medication errors
- May exclude portions of labeling protected by patent or exclusivity

Chemistry Review

Reviewing drug substance and drug product for:

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Product specifications
- Packaging
- Stability

Drug Substance Information

- Most generic drug product manufacturers rely on third parties for supplying drug substances.
- Drug substance suppliers submit Drug Master File (DMF) to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

Drug Master File

Type I: Facilities

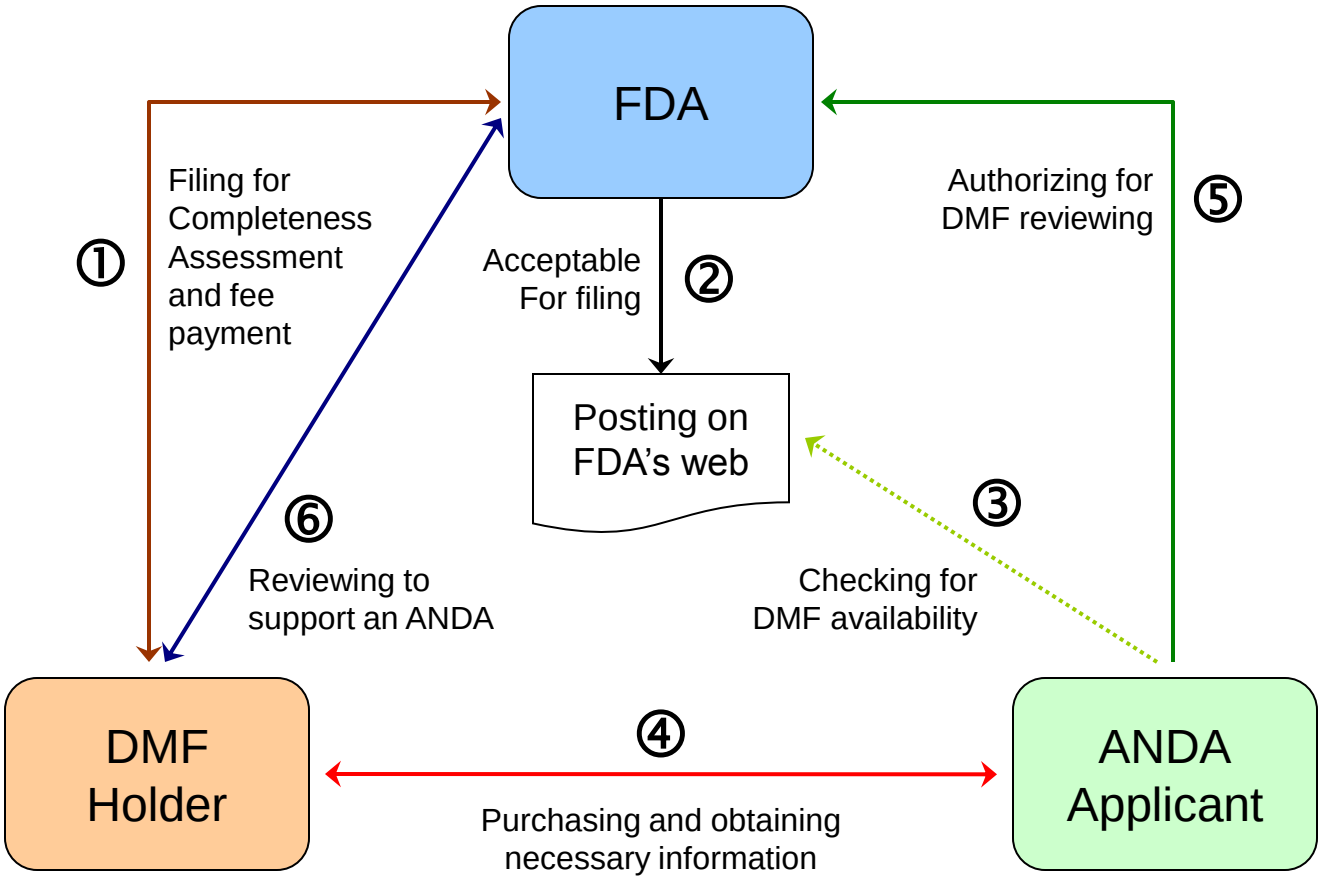
Type II: Drug Substance

Type III: Containers & Closures (Bottles, Caps, Syringes, Stoppers, etc.)

Type IV: Colors, Flavors

Type V: Excipients or Microbiology

Type II DMF Filing/Review Process

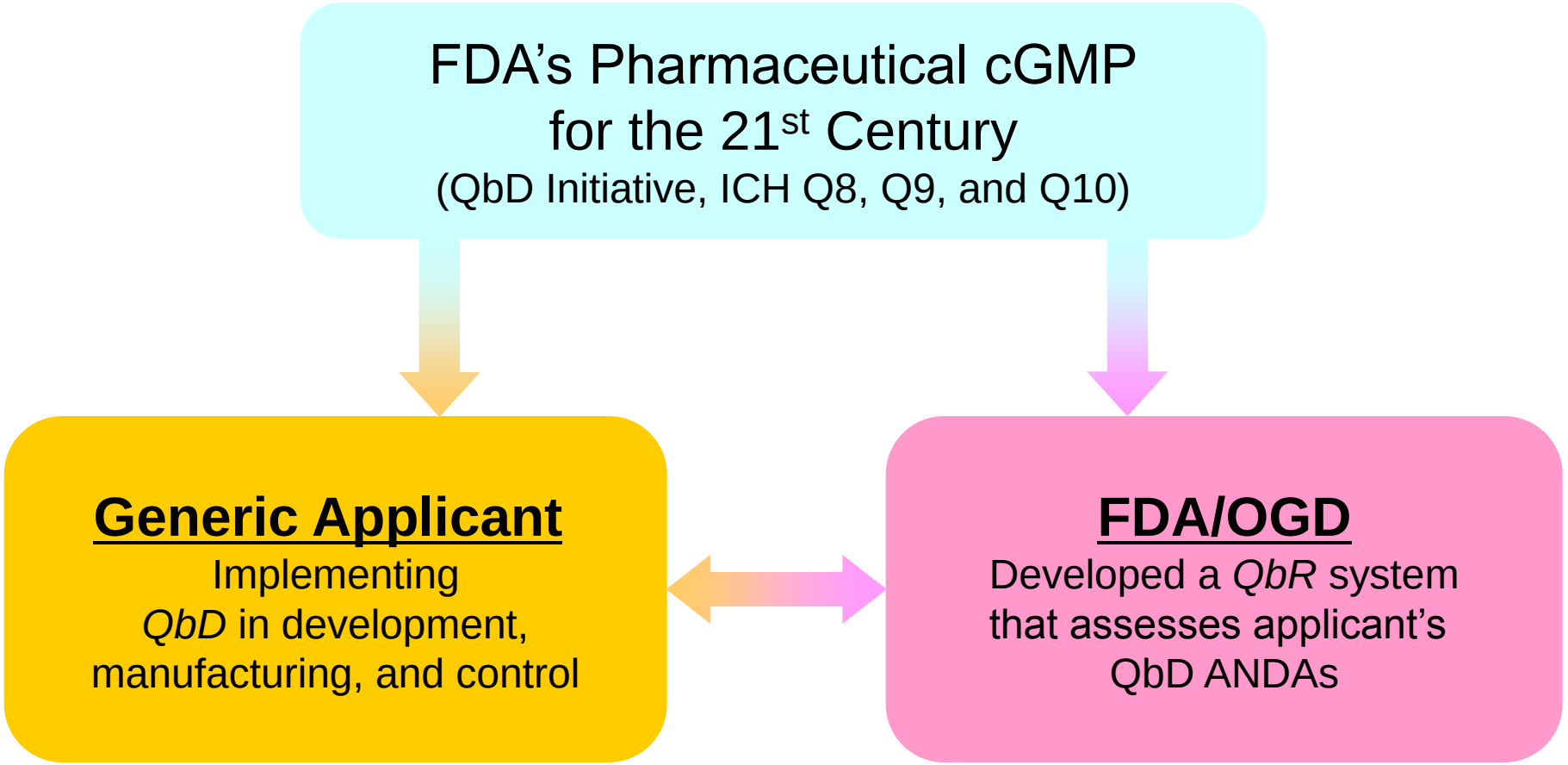


DMF Available for Reference List: http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

DMF Review

- ***DMFs are neither approved nor disapproved.***
- A DMF is reviewed to determine whether it is adequate to support the particular Application that references it.

cGMP for the 21st Century



Quality by Design (QbD) - Paradigm Shift

Past/Present Paradigm

ANDA Formulation/Process Submitted Without Context

Claimed to be Acceptable Based Upon a Passing BE study to the RLD

"Equivalence by Testing"

QbD Paradigm

Systematic approach
QTPP/CQA: predefined target.
Product & process design and understanding: pharmaceutical equivalence to the RLD.
Control strategy: to ensure intended performance be consistently delivered.

Asks Sponsors How They Systemically Arrived at a Bioequivalent Drug Product

"Equivalence by Design"

Question based Review (QbR)

- Implemented for generic drugs in 2007
- QbR is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to:
  - Comprehensively assess critical formulation and manufacturing process variables
  - Set regulatory specifications relevant to quality
  - Determine the level of risk associated with the manufacture and design of the product

QbR Example

Q **What are the unit operations in the drug product manufacturing process?**

A

- Detailed flow chart
  - unit operations (blending, drying, etc),
  - equipment,
  - point of material entry,
  - identification of critical steps (with process or other controls)
- Narrative summary of the manufacturing process
- Reprocessing/reworking statement
- Executed batch record and blank product batch record

Microbiology Review

Reviewing sterile drug products (parenteral, ophthalmic, and inhalation) for:

- Product Development (container/closure integrity validation and preservative effectiveness)
- Overall sterile manufacturing process design and process controls
- Terminal sterilization/aseptic fill process validation
- Drug product specifications
- Release and stability
- Studies to support labeling

Inspection - cGMP/Compliance

- All facilities used for manufacturing, testing, packaging/storing drug substance and drug product are subject for inspections and must be in compliance at the time of approval.
- Inspection program is also design to check data integrity. If data integrity is in question all reviews will stop.
- Type of inspection includes: pre-approval, post-approval, and for cause.

ANDA Approval

All review disciplines find the ANDA acceptable and all facilities are in satisfactory standing as reviewed and inspected.

- Full Approval - all valid patents and exclusivities for the RLD are expired or any legal issues that may block approval of the ANDA are settled.
- Tentative Approval – there exist unexpired patents and exclusivities for the RLD.

“The Orange Book”

Approved Drug Products with Therapeutic Equivalence Evaluations

- Contains list of all FDA approved drug products (NDAs, ANDAs and OTCs)
- Therapeutic equivalence codes
  - “A” = Substitutable
  - “B” = NOT substitutable
- Patent and exclusivity expiration dates
- Reference Listed Drugs - A drug product identified by FDA for generic companies to compare their proposed products

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

Post-Approval Submissions

- Supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities.
  - Prior Approval Supplement (PAS) – major changes
  - Changes Being Effected (CBE) – moderate changes
- Annual report must be submitted each year within 60 days of the anniversary date of approval of the application.
  - May include some minor changes

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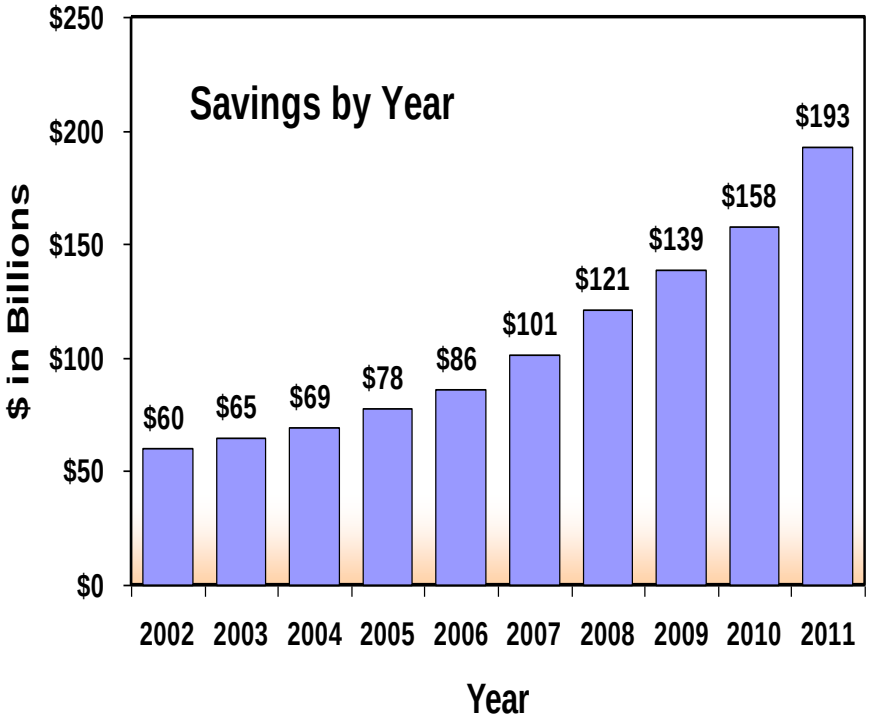
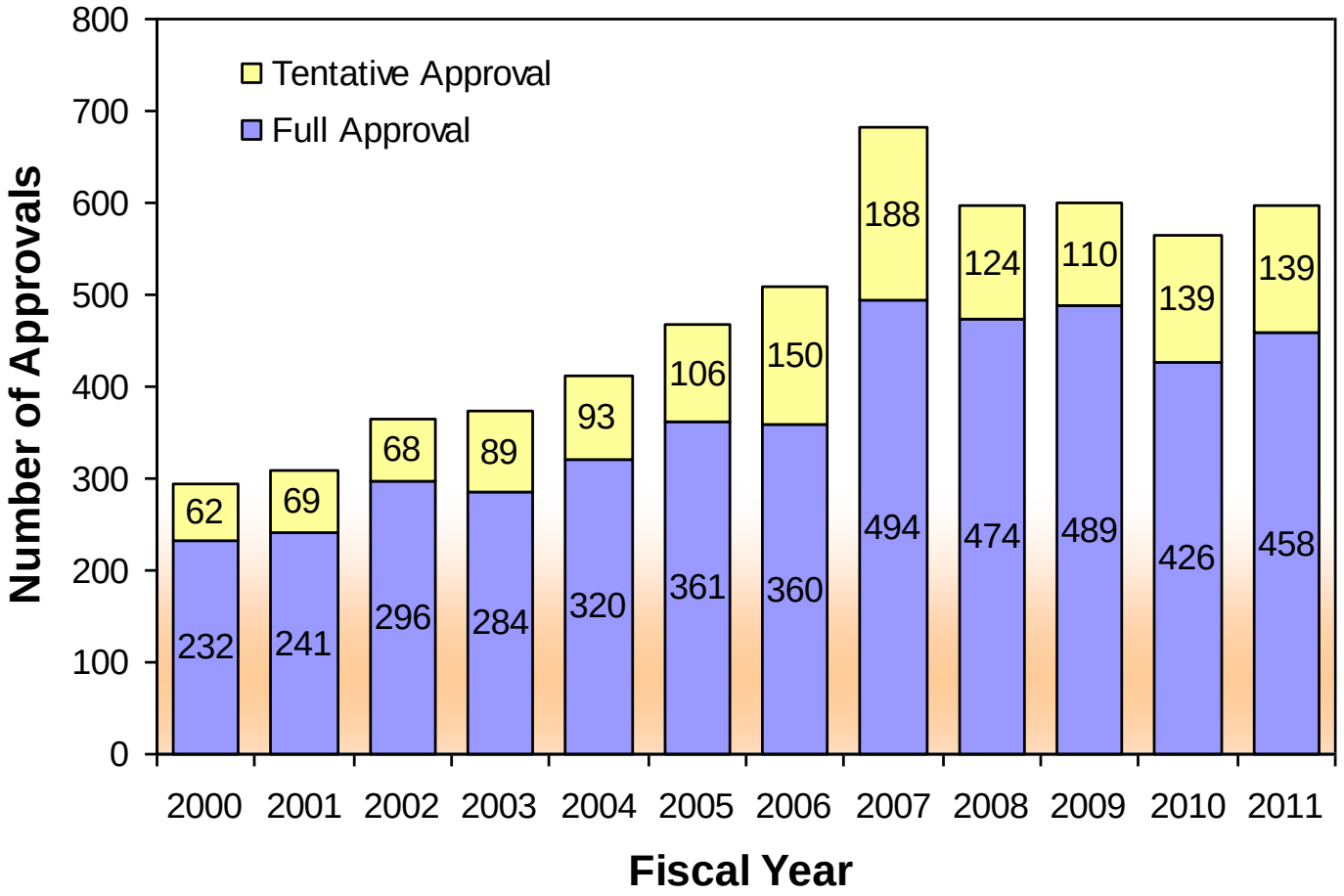
Economic Impact of Generic Drugs

- Generic Drugs account nearly 80 percent of the 4 billion prescriptions written in the U.S. in 2011.
- Generic Drugs cost 30% to 80% less than brand counterparts.



Source: Generic Pharmaceutical Association website (www.gphaonline.org)

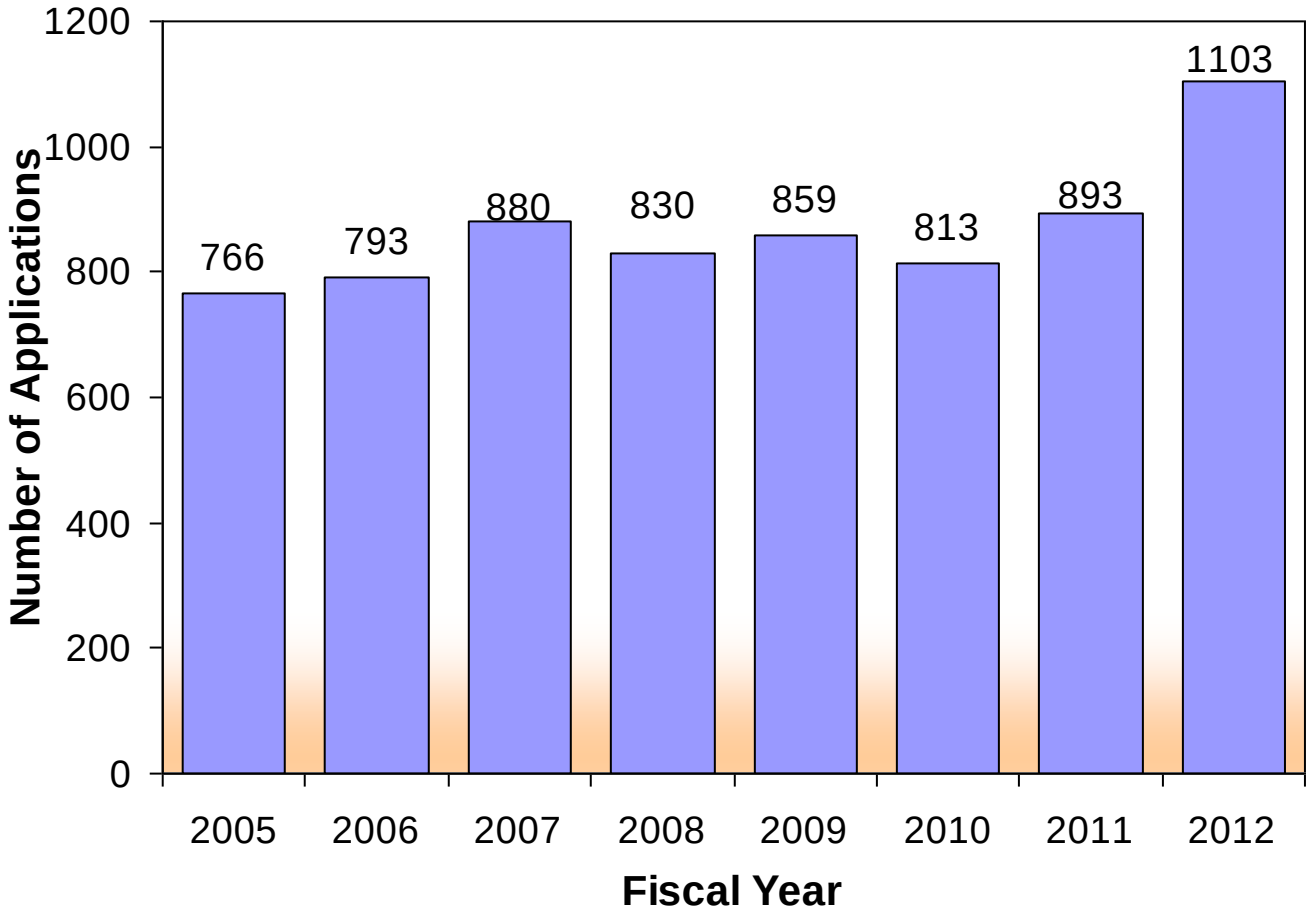
Generic Drug Approvals



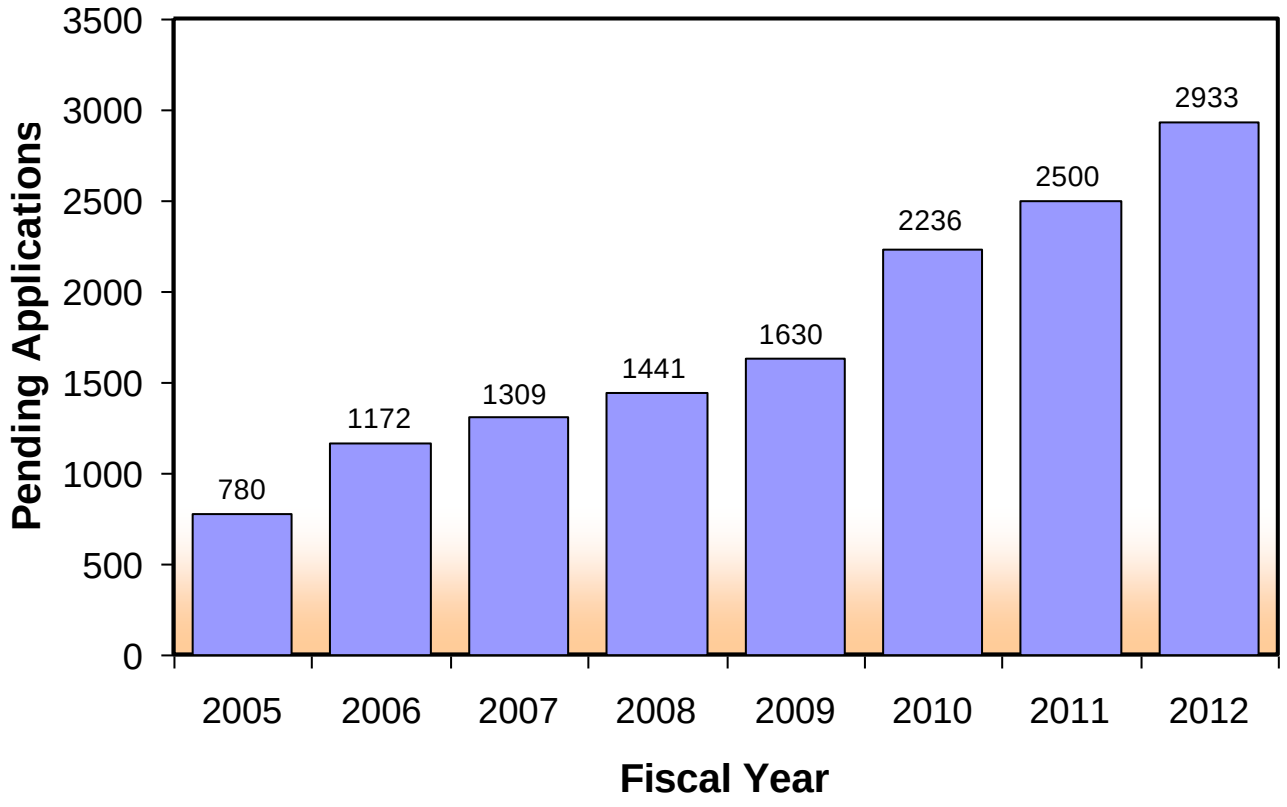
Challenges in Generic Drug Review

- Complex products and dosage forms
- Growing workload
  - Receipt of applications continue to be greater than approvals
  - Increasing complexity of review process
- GDUFA review performance commitments

ANDA Receipts



ANDA Backlog (pending review)



GDUFA Review Performance Goals

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Original ANDA	Expedite review of paragraph IV and maintain pre-GDUFA productivity		60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 first major amendment	Maintain pre-GDUFA productivity		60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 minor amendments (1st – 3rd)	Maintain pre-GDUFA productivity		60% in 3 months*	75% in 3 months*	90% in 3 months*
Tier 1 minor amendments (4th – 5th)	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
Tier 2 amendment	Maintain pre-GDUFA productivity		60% in 12 months	75% in 12 months	90% in 12 months
Prior approval supplements	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
ANDA, amendment, and PAS in backlog on Oct 1st, 2012	Act on 90% by end of FY 2017				
Controlled correspondences	Maintain pre-GDUFA productivity		70% in four months*	70% in two months*	90% in two months*

*10 months if inspection required

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GDUFA Hiring

- Additional resources are need to enable the FDA to reduce a current backlog of pending drug applications and cut the average review time required.
  - Microbiologist
  - Chemist
  - Chemical Engineer
  - Consumer Safety Officer
  - Pharmacist
  - Medical Officer
  - Operations Research Analyst
  - Interdisciplinary Scientist
  - Regulatory Counsel

Hiring Goals

- 25% in FY-13
- 50% in FY-14
- 25% in FY-15

More detailed information and coming virtual hiring event can be found online at the FDA Hiring Initiative webpage:

http://www.fda.gov/AboutFDA/WorkingatFDA/GenericDrugUserFeeHiring/default.htm


Generic Drugs
Safe. Effective. FDA Approved.
Consistent labeling
Rigorous manufacturing standards
Assured quality
Purity check
Performance evaluation
Same drug
Visit www.fda.gov/cder/ or call 1-888-INFO-FDA to learn more.
FDA
U.S. Department of Health and Human Services
Food and Drug Administration


Thank You!