Generic Labeling 2006

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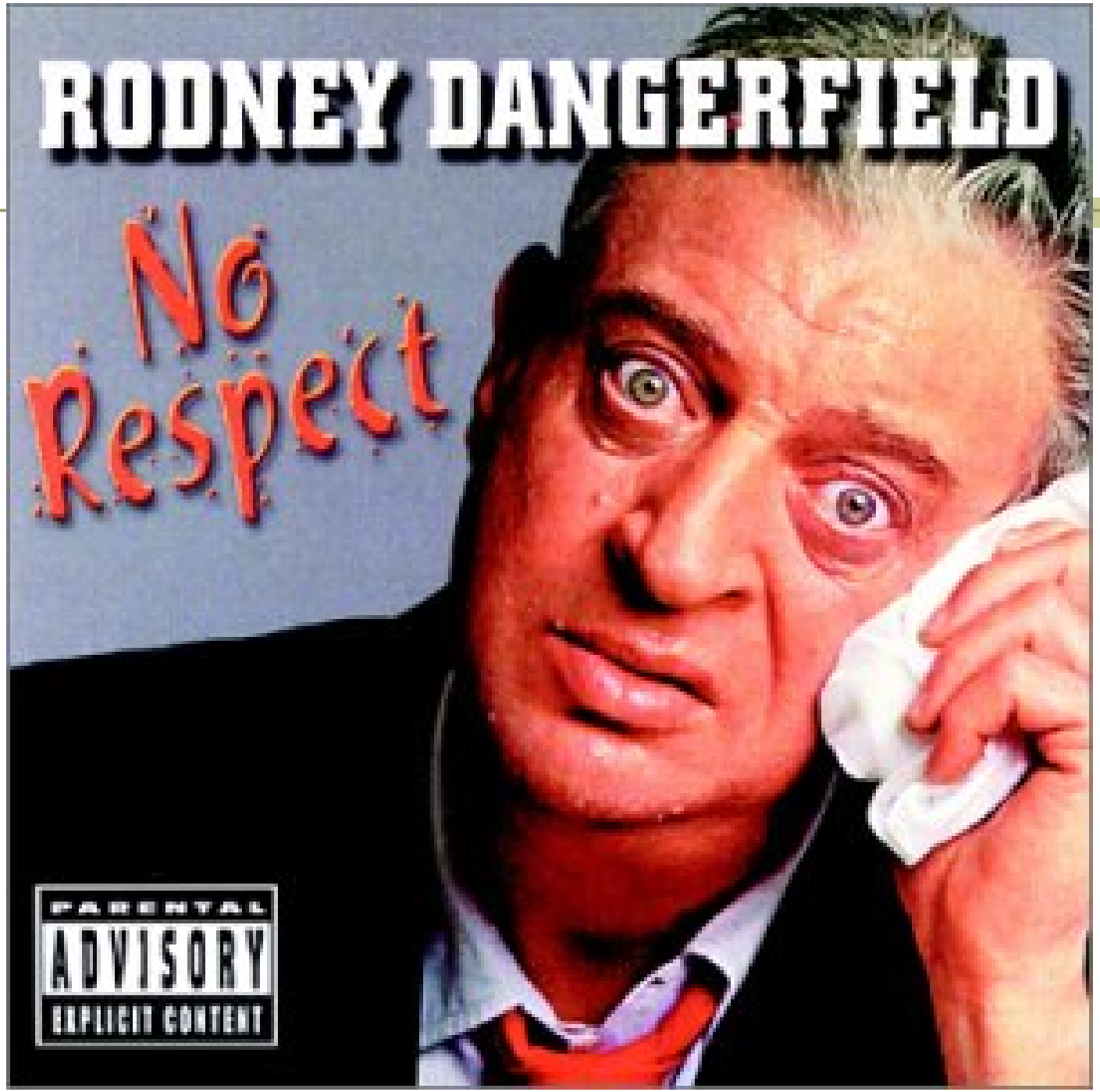
RODNEY DANGERFIELD
No Respect
PARENTAL
ADVISORY
EXPLICIT CONTENT

"I think labeling is a complete waste of time,“… "It's much beloved by industry, it's much beloved by FDA and it's much beloved by lawyers, but it's worthless nonetheless."

The Pink Sheets
January 23, 2006
Volume 68 | Number 004 | page 8

"…studies show that fewer than one in 10 physicians routinely read drug labels, which provide the most complete information about a drug's dangers and uses."

The New York Times
"New Drug Label Rule Is Intended to Reduce Medical Errors"
By Gardiner Harris | January 19, 2006

Changes in Labeling

- Best Pharmaceuticals for Children's Act
- The Electronic Labeling Rule
- Structured Product Labeling
- Physician Labeling Rule

“Same As” Principle

- 505(j)(2)(A) An abbreviated application for a new drug shall contain-
  - (v) – information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers.

21 CFR 314.94(8)

Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

Pediatric Exclusivity Dilemma For Generics

When information protected by pediatric exclusivity is carved out, the generic product ends up misbranded because the labeling is not in compliance with 21 CFR 201.57(f)(9) which pertains the "Pediatric use" subsection of the PRECAUTIONS section.

Best Pharmaceuticals For Children's Act (BPCA)

Signed into law on January 4, 2002.

Amended the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children.

Best Pharmaceuticals For Children's Act (BPCA)

- Section 11 of the Act addresses the prompt approval of drugs under section 505(j) when pediatric information is added to the label.
- Item (2) of this section states that the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling… include –
  - "(A) a statement that, because of marketing exclusivity for a manufacturer-- (i) the drug is not labeled for pediatric use… and
  - (B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary."

Creating a Model Labeling For Generics under BPCA

1. Consults the pediatric committee.
2. Incorporate the comments from the pediatric committee & consult the new drug reviewing division.
3. Incorporate both the pediatric committee & the new drug reviewing division's comments & consult Office of Chief Counsel (OCC).
4. Meet with representatives from the pediatric committee, new drugs, & OCC.

Consult to the Pediatric Committee

CONSULT TABLE : Comparison of Zofran Injection Labeling Previously Approved on November 24, 2004, Recently Approved on March 25, 2005, and OGD's Proposed Labeling for "Generic Zofran"

PREVIOUS INSERT TEXT SLR-034 (AP November 24, 2004) Underline indicates revisions in the new approved labeling	NEW INSERT TEXT with Pediatric INFORMATION from S-025 (APPROVED March 25, 2005) Highlighted text indicates new approved language and highlighted text with ~~strikeouts~~ are proposed text for carve out.	OGD's Proposed Tex for "Generic Zofran Injection" proeucts.	COMMENTS, RECOMMENDATIONS & PROPOSED TEXT DRAFTED BY THE OFFICE OF GENERIC DRUGS (OGD)
CLINICAL PHARMACOLOGY **Pharmacodynamics:** Ondansetron is a selective 5-HT$_3$ receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT$_3$ type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action in chemotherapy-induced ~~emesis~~ is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of ~~emesis~~. The released serotonin may stimulate the vagal afferents through the 5-HT$_3$ receptors and initiate the vomiting reflex. In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT$_3$ receptor antagonist. In normal volunteers, single I.V. doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.	CLINICAL PHARMACOLOGY **Pharmacodynamics:** Ondansetron is a selective 5-HT$_3$ receptor antagonist. 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1

Consult to New Drug Reviewing Division

CONSULT TABLE : Comparison of Zofran Injection Labeling Previously Approved on November 24, 2004, Recently Approved on March 25, 2005, and OGD's Proposed Labeling for "Generic Zofran"

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Consult to Office of Chief Counsel

CONSULT TABLE : Comparison of Zofran Injection Labeling Previously Approved on November 24, 2004, Recently Approved on March 25, 2005, OGD's Proposed Labeling for "Generic Zofran", Division of Pediatric Drug Development (DPDD) Recommendations and Division of Gastrointestinal and Coagulation Drug Products (DGCDP)

PREVIOUS INSERT TEXT SLR-034 (AP November 24, 2004) Underline indicates revisions in the new approved labeling	NEW INSERT TEXT with Pediatric INFORMATION from S-026 (APPROVED March 25, 2005) Highlighted text indicates new approved language and	Text with ~~strikeouts~~ are proposed for carve out and the underlined text are replacement statements recommended by OGD.	Revised based on Division of Pediatric Drug Development Recommendation Memorandum dated June 6, 2006	Revised based on the Division of Gastrointestinal	Comments
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TIME

- Creating the Model Labeling is time consuming.
  - Preparing Consults
  - Waiting for the completed reviews of the consults.
  - Scheduling meetings
  - Preparing the final model labeling
  - Disseminating the model labeling
- Usually takes months to create the model.
- OGD is working to streamline this process.

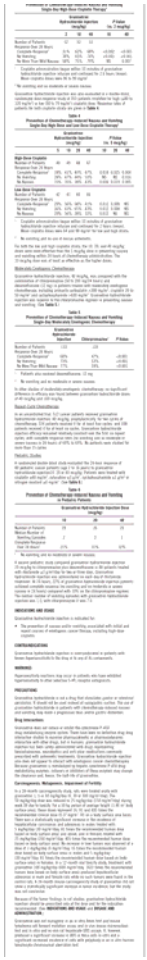
The Electronic Labeling Rule

- Effective June 8, 2004
- Requires that “the content of labeling be submitted electronically in a form that FDA can process, review, and archive”.

Portable Document Format (PDF) Attributes

- Can be used in Adobe for comparison
- Can be used to submit final printed labeling in place of 12 paper copies.

PDF Limitation



Structured Product Labeling (SPL)

- Implemented on October 31, 2005
- It is the electronic form that FDA has adopted to process, review, and archive the insert labeling.
- SPL is the content of labeling in a standardized electronic file format with tagged blocks of text and data elements in XML.

Purpose of SPL

- Improve patient safety through accessible drug product information
- Support initiatives to improve patient care by better management of health care information
  - Electronic prescribing
  - Possibly the electronic health record (EHR), which will provide health care providers, patients, and other authorized users access to patient information in electronic format
  - The DailyMed, a new way to distribute up-to-date and comprehensive medication information in a computerized format for use in health care information systems.
  - Decision support systems
- Meets the mandate in Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)

SPL Advantages over PDF

- The exchange of labeling changes with SPL will become much easier and more efficient for both FDA and manufacturers. For example, with SPL, only the sections or data elements of the labeling that are changed needs to be submitted rather than the entire insert labeling.
- SPL can be used to exchange information needed for drug listing, thus eliminating redundant data collection and improving efficiency.

Status of SPL Submissions

- Number of SPL loaded in the ELIPS is____.
- Approximately 80% of SPLs are rejected due to validation problems.
- For generics that are not listed as the reference listed drug, the option to submit SPL within 30 days after the RLD SPL is posted on the DailyMed website is still in effect.

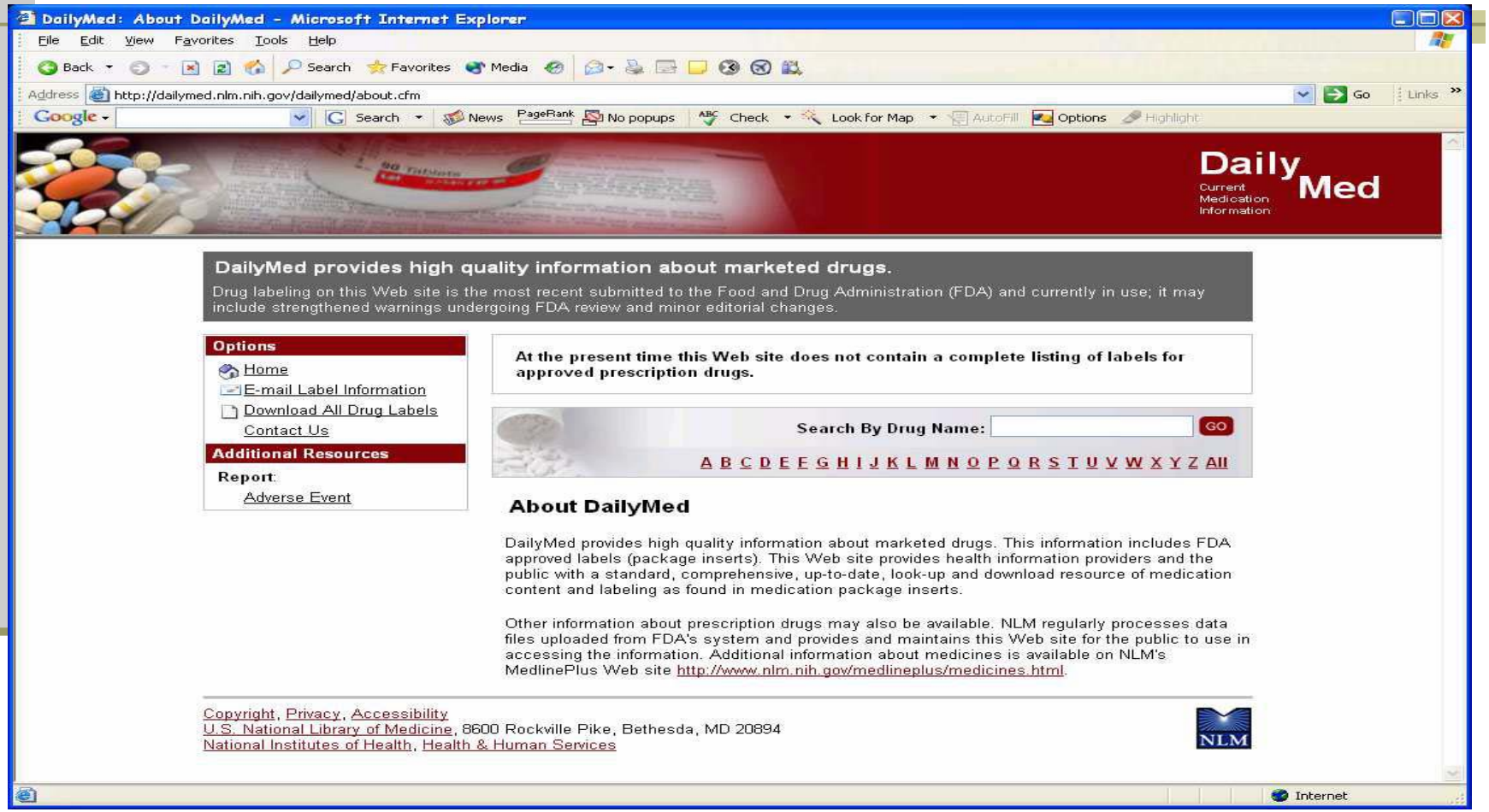
ELIPS

- Electronic Labeling Information Processing System (ELIPS)
  - Designed and constructed by Northrop-Grumman
  - Contracted & Implemented by OIT
  - ELIPS is the system the labeling reviewers will use to review and process SPL.

ELIPS

- Scans Electronic Document Room (EDR)
  - Every 5 minutes
  - Validation (Tier 2) of SPL
- Validates the labeling for SPL standards
- Puts copy of SPL into ELIPS label repository
- Assigns Label Coordinator and Reviewers to Labeling
- Allows editing of the SPL
- Allows transmission of SPL to the National Library of Medicine

DailyMed Web Site



http://dailymed.nlm.nih.gov/dailymed/about.cfm

Things to Remember When Submitting SPL

- Place the electronic media immediately after the cover letter.
- Continue submitting side by side annotated labeling.
- Continue submitting final printed labeling for approval.
- Continue submitting a MS Word version of the insert labeling.

SPL Resources

http://www.fda.gov/oc/datacouncil/spl.html

Physician Labeling Rule

- Effective on June 30, 2006
- PLR is the first major change in the insert labeling in 25 years.
- It is designed to make the insert labeling easier to read and understand.
- Addition of Highlights and Table of Contents
- Revision and Reorganization of the section of the insert labeling.

Highlights

- Recent Labeling Changes
- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- HOW SUPPLIED
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
- MedWatch phone number for patients to report adverse drug reactions

Example of Fictional Highlights of Prescribing Information Based on Physician Labeling Rule

OCRACEPHALOSE® [fictional drug] Rx
(spurilous hypothetic chloride) Tablets or Capsules for oral use [fictional drug]

----------RECENT LABELING CHANGES----------
Warnings/Precautions, Depression (5.3)

----------INDICATIONS AND USAGE----------
Adjunct therapy with a sulfonylurea to lower blood glucose in patients with Type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise (1.1)

----------DOSAGE AND ADMINISTRATION----------
Initial dose is 100 mg once every morning and may be titrated up to 300mg (2.1)

----------HOW SUPPLIED----------
Tablets: 100 mg (3)
Capsules: 100 mg (3)

----------CONTRAINDICATIONS----------
Hepatic impairment (4)

----------WARNINGS/PRECAUTIONS----------

Hepatic dysfunction leading to acute liver failure may occur, typically within 3 months of initiation (5.2)
Evaluate liver function prior to initiating Ocracephalose and monitor weekly for 3 months. Discontinue if LFTs increase > 3 times upper limit of normal (5.2)

Severe depression with suicidal ideation occurred in 2% of patients. Discontinue Ocracephalose or initiate antidepressant therapy if depression occurs (5.3)
Hypoglycemia can occur with insufficient caloric intake and use of alcohol (5.5, 6.2)

Most Common Adverse Reactions (> 5%) (8)
somnolence, dry mouth, nightmares, and sexual disorders

To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone#) or FDA's MedWatch at 1-800-FDA-1088

----------DRUG INTERACTIONS----------
Domecattus reduce domecattus dose by one-half (5.4, 6.1)
Alcohol: increases incidence of hypoglycemia (6.2)

----------USE IN SPECIFIC POPULATIONS----------
Hepatic impairment: Contraindicated in patients with hepatic impairment (4, 7.6)

---See P for PATIENT COUNSELING INFORMATION and --- Ocracephalose's approved patient labeling

These highlights do not include all the information needed to prescribe Ocracephalose safely and effectively. See Ocracephalose's comprehensiveprescribing information provided below.

Revised: 12/2003

Effect of PLR on Generics

- Generics still need to be the same as the RLD.
- PLR will most likely be posted in SPL

PLR Implementation Plan

TABLE 5.—IMPLEMENTATION PLAN

Applications (NDAs, BLAs, and Efficacy Supplements) Required to Conform to New Labeling Requirements	Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval
Applications submitted on or after June 30, 2006	Time of submission
Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006	June 30, 2009
Applications approved 1 to 2 years before June 30, 2006	June 30, 2010
Applications approved 2 to 3 years before June 30, 2006	June 30, 2011
Applications approved 3 to 4 years before June 30, 2006	June 30, 2012
Applications approved 4 to 5 years before June 30, 2006	June 30, 2013
Applications approved more than 5 years before June 30, 2006	Voluntarily at any time

What Next? Do we need FPL?

YES!

However…

Challenges For the Labeling Review Branch

1. Increased workload

2. SPL: Learning new system, reviewing data elements and managing the release of SPL to NLM

3. Complicated patent and exclusivity issues

Challenge # 1

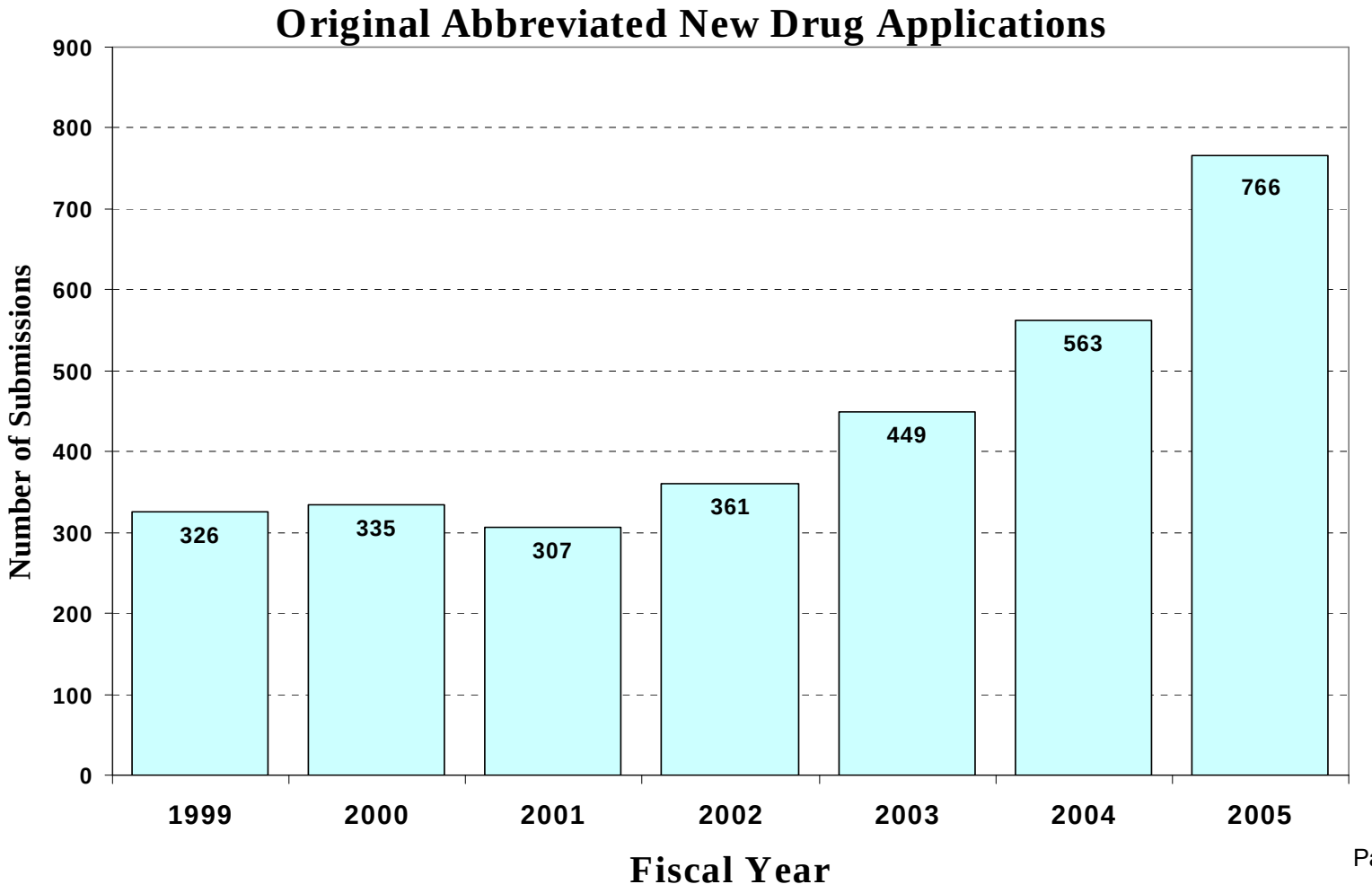
washingtonpost.com

Generic Drugs Hit Backlog At FDA

No Plans to Expand Review Capabilities

By Marc Kaufman
Washington Post Staff Writer
Saturday, February 4, 2006; A01

Workload


Original Abbreviated New Drug Applications
Number of Submissions
900
800
700
600
500
400
300
200
100
0
326
335
307
361
449
563
766
1999
2000
2001
2002
2003
2004
2005
Fiscal Year

OGD Labeling Review Branch

John Grace (Team Leader)

- Angela Payne
- James Barlow
- Ruby Wu
- Postelle Birch
- Beverly Weitzman
- Ann Vu

Lillie Golson (Team Leader)

- Adolph Vezza
- Chan Park
- Jacqueline Counsel
- Melaine Shin
- Michelle Dillahunt
- Koung Lee

Challenge # 2

- SPL
  - Learning how to use ELIPS
  - Processing SPL
  - Managing SPL
  - Establishing SPL Legacy Labeling

Challenge # 3

- Patent and Exclusivity
  - Complicated
  - Time Consuming
  - PLR

How Can Industry Help?

- Submit SPL
- Submit all labeling electronically
- Submit supporting labeling information electronically
- Notify labeling reviewers when amending patent certifications
- Submit Side by Side annotated labeling with detail explanation of the differences.
- Check Drugs@FDA website

Supporting Labeling Information

- Component and Composition
- Patent certification and Exclusivity statement
- Conditions used to collect stability data (e.g.,Temperature and RH)
- Container/Closure system (including light transmission test if applicable)
- Provide an accurate description of the solid oral dosage form or provide a picture or image depicting actual size and color.
- Identify the manufacturer

SUMMARY

Significant Changes in labeling at the turn of the century have created an environment to improve dissemination of updated drug information and allow for better utilization of that information.

The Labeling Review Branch has challenges but with new technology, new regulations, and support from industry and upper management, I think we'll be able to review labeling more efficiently and help approve generic applications when they become eligible for approval.