Generic Labeling 2006

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"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."
“…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.
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.
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.
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

<table>
<thead>
<tr>
<th>PREVIOUS INSERT TEXT</th>
<th>NEW INSERT TEXT WITH PEDIATRIC INFORMATION</th>
<th>OGD’s Proposed Text for “Generic Zofran Injection” Products</th>
<th>COMMENTS, RECOMMENDATIONS &amp; PROPOSED TEXT DRAFTED BY THE OFFICE OF GENERIC DRUGS (OGD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR-324 (AP November 24, 2004) Underline indicated revisions in the new approved labeling</td>
<td><strong>Highlighted text indicates new approved language. Underline indicates text with asterisks are proposed text for carve out.</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CLINICAL PHARMACOLOGY

**Pharmacodynamics:** Ondansetron is a selective 5-HT3 receptor antagonist. While ondansetron’s mechanism of action has not been fully characterized, it is not a dopamine-receptor agonist. Serotonin receptors of the 5-HT3 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 antinausea action is mediated centrally, peripherally, or in both areas. However, cytoxic 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 ondansetron administration in parallel with the onset of anorexia. The released serotonin may stimulate the vagal afferents through the 5-HT3 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 adrenergic vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT3 receptor antagonist.

In normal volunteers, single i.v. doses of 0.15 mg/kg of ondansetron had no effect on emetogenic activity, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 15-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.

No replacement statement necessary.

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No replacement statement necessary.
### Consult to New Drug Reviewing Division

#### Clinical Pharmacology

**Pharmacodynamics:**

Consultation is a selective 5-HT₃ receptor antagonist. While administration of consultation has not been thoroughly characterized, it is not a competitive inhibitor for any other receptors. Consultation is selectively present both peripherally on vagal afferents and centrally in the chemoreceptor trigger zone of the medulla. It is not certain whether consultation’s mechanism of action is chemosensory-mediated, as it is incapable of carrying out either chemosensory or meningitis-mediated stimuli, peripherally or centrally. However, consultation is chemosensory receptor antagonist, and its effect on the vagal reflex is the mechanism of action through the 5-HT₃ receptors.

In animals, the vagal response to consultation can be prevented by pretreatment with an inhibitor of serotonin synthesis, and bilateral vagal ablation. Consultation is effective against consultation-induced nausea, vomiting, and diarrhea.

In normal volunteers, single V.O. dose of 40 mg/kg of consultation had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit. In another study in six normal male volunteers, a 10 mg dose induced over 5 minutes showed no effect on the drug on gastric emptying, heart rate, ETOG level, blood pressure, or electrocardiogram (ECG).

Consultation has no effect on plasma protein concentrations.

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### Table: Comparison of Zofran Injection Labelling Recently Approved on November 24, 2004, Recently Approved on March 25, 2005, and OGD's Proposed Labelling for "Gastic Zofran"

<table>
<thead>
<tr>
<th>Previous Insert Text</th>
<th>New Insert Text with Problem Information from 3-026</th>
<th>OGD's Version</th>
<th>Recommendation from the Division of Pediatric Drug Development</th>
<th>Comments: Recommendation &amp; Proposed Text Drafted by the Office of Generic Drugs (OGD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation is a selective 5-HT₃ receptor antagonist. While administration of consultation has not been thoroughly characterized, it is not a competitive inhibitor for any other receptors. Consultation is selectively present both peripherally on vagal afferents and centrally in the chemoreceptor trigger zone of the medulla. It is not certain whether consultation’s mechanism of action is chemosensory-mediated, as it is incapable of carrying out either chemosensory or meningitis-mediated stimuli, peripherally or centrally. However, consultation is chemosensory receptor antagonist, and its effect on the vagal reflex is the mechanism of action through the 5-HT₃ receptors.</td>
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**Clinical Pharmacology**

**Pharmacodynamics:** Ondansetron is a selective 5-HT3 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-HT3 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 action in chemotherapyna-induced nausea and vomiting is mediated centrally, peripherally, or in both sites. However, serotonin chemoreceptor appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, serotonin (5-HT) (5-hydroxytryptamine) causes increases after cholinergic administration in parallel with the onset of vomiting. The released serotonin can stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex. (Penultimate paragraph in the "Pharmacodynamics" subsection)

In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the pharmacokinetics model of nausea and vomiting. This is similar to the prevention of nausea and vomiting using the pharmacokinetics model of nausea and vomiting.

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**Consult Table: Comparison of Zofran Injection Labeling Previously Approved on November 24, 2004.**

Recently Approved on March 22, 2005, OGD's Proposed Labeling for "Generic Zofran," Division of Pediatric Drug Development (DPDD) Recommendations and Division of Gastrointestinal and Congestive Drug Products (DGCDP)

<table>
<thead>
<tr>
<th>Previous Insert Text</th>
<th>New Insert Text with Parent Information from S-026</th>
<th>Text with underlines are proposed for carve out and the underlined text are replacement statements recommended by OGD.</th>
<th>Revised based on Division of Pediatric Drug Development Recommendation Memorandum dated June 6, 2006</th>
<th>Revised based on the Division of Gastrointestinal and Congestive Drug Products (DGCDP)</th>
<th>Comments</th>
</tr>
</thead>
</table>

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**Consult to Office of Chief Counsel**
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

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
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<tr>
<td>Data 13</td>
<td>Data 14</td>
<td>Data 15</td>
<td>Data 16</td>
</tr>
</tbody>
</table>

Note: The table above represents the table content on the page.
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-----------------------------
Domecatus reduce domecatus 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 ---
Ocrapephalose’s approved patient labeling

These highlights do not include all the information needed to prescribe Ocracephalose safely and effectively. See Ocracephalose’s comprehensive prescribing 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
<table>
<thead>
<tr>
<th>Applications (NDAs, BLAs, and Efficacy Supplements) Required to Conform to New Labeling Requirements</th>
<th>Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval</th>
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<tbody>
<tr>
<td>Applications submitted on or after June 30, 2006</td>
<td>Time of submission</td>
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<tr>
<td>Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006</td>
<td>June 30, 2009</td>
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<tr>
<td>Applications approved 1 to 2 years before June 30, 2006</td>
<td>June 30, 2010</td>
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<tr>
<td>Applications approved 2 to 3 years before June 30, 2006</td>
<td>June 30, 2011</td>
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<td>Applications approved 3 to 4 years before June 30, 2006</td>
<td>June 30, 2012</td>
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<td>Applications approved 4 to 5 years before June 30, 2006</td>
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<td>Applications approved more than 5 years before June 30, 2006</td>
<td>Voluntarily at any time</td>
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</table>
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

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

<table>
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<tr>
<th>Fiscal Year</th>
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</table>
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.