Labeling Updates and Overview

GPhA/FDA Fall Technical Conference

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# Labeling Review Branch

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**Carrie Lemley is the labeling review branch project manager**
Who We Are

- **Pharmacists** – Some with Clinical Experience and some with Community Rx Experience (some with both). Some still currently working on the front lines....

- Applying our experiences in the workplace to safety in labeling
What we do

- Pharmacy practice issues, especially relating to safety and the prevention of medication errors

- Ensure that the proposed ANDA labeling is “the same as” the last approved labeling for the Reference Listed Drug (RLD) except for differences allowed by the regulations
  - Section 505(j)(2)(A)(v) of the Act
  - 21 CFR 314.94(a)(8)
TOPICS

- H.R. 3590, the Patient Protection and Affordable Care Act (the PPACA)
- REMS and Safety Labeling (Update)
- QbLR follow-up
- General Reminders and Information
OVERVIEW of Patient Protection and Affordable Care Act

- **Background**

- Signed into law March 23, 2010 (Public Law H.R. 3590)

- PRIOR to PPACA, ANDA products were required to have the same labeling as the reference listed drug (RLD) EXCEPT for differences allowed by section 505 (j)(2)(A)(v) of the FD&C Act and Title 21 Code of Regulations (CFR) 314.94(a)(8). Therefore, when last minute labeling revisions were approved for the reference listed drug prior to generics being eligible for approval, sometimes the approval of ANDAs were delayed.

**CONSEQUENCES –**

- Cost to the Applicants
- Cost to the tax payers
- Additional review time
- Frustration/Anger
- Confusion
- Feeling as if you may never SEE that ever so elusive...
Resulting in possible
Section 10609 of the PPACA added section 505(j)(10) to the FD&C Act permitting the following:

APPROVAL of an ANDA even if the reference Listed Drug’s labeling is DIFFERENT in certain cases
The FDA may approve an ANDA, even though labeling changes have been made to the reference listed drug, if all of the three following criteria are met:

- The approval of the RLD’s labeling revision is made within 60 days before the expiration of the patent, exclusivity period, or a 30-month stay delaying ANDA approval.

- The approved revision to the labeling of the RLD does not include a change to the “WARNINGS” section (the physician labeling rule format consolidates the “WARNINGS and PRECAUTIONS” section). and

- The FDA has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug product.
If the THREE required criteria are met -

- The ANDA sponsor(s) can provide a letter of commitment to submit a “Supplement” containing the revised labeling no later than 60 days from the date of notification. Once this is established....

- The labeling project manager (PM) will use the FDA Document Archiving Reporting and Regulatory Tracking System (DARRTS) to track the fulfillment of agreements within the specified time frame.
References

- Patient Protection and Affordable Care Act (the PPACA) (Amendment No 2786). See http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590ENR/html/BILLS-111hr3590ENR.htm
REMS and Safety Labeling Changes
OVERVIEW of FDA Amendments Act (FDAAA)

(as it pertains to safety labeling and REMS)

Signed into law September 27, 2007 (Public Law 110-85)

Goals of FDAAA

- Enhance medical product safety
- Better inform the public about drug safety
- Provide new tools for FDA to reduce risks and minimize unsafe drug use.
FDAAA Title IX: DRUG SAFETY

New authorities to compliance: (Strict timelines)

- **Require** sponsors to make safety labeling changes based on “new safety information” *(505(o)(4) of FDCA)*

- **Require** sponsors to develop and comply with risk evaluation and mitigation strategies *(REMS (505-1 of FDCA))*
Discontinued vs Withdrawn Requirements

- If Withdrawn per Federal Register Notice, no action required

- Application must be in the Discontinued section of the Orange Book – (our source)
  - If you receive a letter, check to see how your application is listed
  - If Need to update labeling but they can be submitted in draft
  - We will issue a CR letter explaining it cannot be approved until FPL is submitted – No response is required from company until firm wants to market the product again.
Risk Evaluation and Mitigation Strategies (REMS)
REMS ELEMENTS

**REMS Elements:**

- Patient Package Insert
- Medication Guides (505-1(e))
- Communication plan (e.g., Dear Health Care Provider letter) (505-1(e))
- Elements to assure safe use (505-1(f)(3)) (formerly called “restricted distribution systems”)
  - Two examples of drugs with restricted distribution systems are thalidomide and isotretinoin.
- Implementation system (505-1(f)(4))
What is a REMS Release?

RLD ANDA
- Sponsor must submit a REMS modification proposal and a REMS assessment
- A review of the assessment will be completed and the Office will either issue a REMS modification approval letter or a CR letter if the FDA determines the REMS is still necessary
- Submit PAS

RLD NDA
- NDAs REMS plan has been released
- Advice letter issued to generic firms requesting supplement
- Submit CBE
Resources

Additional resources regarding REMS:

- FDA Regulatory Information Page: Food and Drug Administration Amendments Act (FDAAA) of 2007

- Questions and Answers on the Federal Register Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies

- Approved Risk Evaluation and Mitigation Strategies (REMS)

- Medication Guides Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) Draft Guidance
QUESTIONED based LABELING REVIEW (QbLR)

- Compiling all the questions and reviewing
- Expecting a Fall 2012 release
Proprietary Names


- Suggestion for expediting your drug product approval

  - If your proprietary name request is holding up approval, you have the option of submitting an amendment utilizing the established drug name for review. However, do NOT withdraw the proprietary name request. Therefore, your ANDA can be approved with the established name.

  - Following approval of your application, you must submit a labeling supplement for the proprietary name and in the cover letter state that this proprietary name is already under review with DMEPA. This will ensure your place in the review process with DMEPA and avoid a longer wait period.
Suggestions/Reminders for your ANDA Submission

- Submit patent and exclusivity information electronically

- Gateway submissions: Ensure the date on the electronic form and cover letter match the date you intend to hit the send button (note: submission received after 4:30 EST or on a weekend/holiday is considered received the next business day)
Suggestions/Reminders for your Labeling Submission

- Submit labels and labeling electronically, including:
  - Cover Letter
  - 356H Form
  - Deficiency-Response point by point
  - Proposed labels and labeling
  - Side-by-side comparison
  - Miscellaneous correspondence

- Cover letter: include information such as
  - Changes in patent/exclusivity statements
  - Changes in other sections of your ANDA and how the changes impact your labeling
  - Medication Guide - describe how many Medication Guides will be provided with each package size
Suggestions/Reminders for your Labeling Submission

- Submit each labeling piece as a separate file

- Final printed labels (FPL)
  - Must be actual color, size and clarity (exception: carton labeling is not required to be actual size)
  - Do not name the file “draft”

- Insert:
  - Ensure that PDF are text based, not image based
  - Submit the insert labeling in Final Print and Microsoft Word format
Suggestions/Reminders for your Labeling Submission

SUPPLEMENTS

- Cover letter
  - Include the proposed implementation date
  - State the changes being proposed
  - Ensure that submissions are properly and clearly titled
    - Complete Response
    - Proposed REMS
    - CBE
    - PAS

- Provide annotated side-by-side comparison against your approved labeling UNLESS new labeling is approved for the RLD

- Do not combine Safety Labeling/REMS supplements with chemistry supplements AND/OR other labeling changes. Make it specific.
Suggestions/Reminders for Container Labels

- Established name and strength should be prominently displayed on the principal display panel


- If an oral solution is subject of a USP monograph, but the RLD states syrup, then the name of the drug product should state “syrup” with “oral solution” in parentheses

- Controlled substance symbol should be clear and large enough to read easily

- Use the correct controlled room storage temperature statement (e.g., Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature])
Suggestions/Reminders for Container Labels

- Differentiate your drug products of different strengths
- Color codes should not conflict with those of the RLD
- Related ANDAs: Strengths and product labels should be well differentiated from one another to prevent product selection error
  - Proximity of Products on the Pharmacy Shelf
  - Shared Dosage Form
  - Same Strength
  - Same Route of Administration
  - Same (or similar) active ingredient name
Suggestions/Reminders for the Expression of Strength

- Separate the strength and net quantity statement

- If the established name is the active moiety and salt (e.g. alendronate sodium) but the strength is based on the base of the active moiety (e.g. alendronate), then you need to add the asterisk after the expression of strength and before the “Each XX contains” statement.
Suggestions/Reminders for Injectables

- The strength per total volume should be followed in close proximity by strength per mL enclosed by parentheses. **400 mg/10 mL** (40 mg/mL)

- Volumes less than 1 mL—The strength per fraction of a mL should be the only expression of strength (e.g., 4 mg/0.5 mL)

- Lyophilized product: express strength as “XX mg/vial”

- Include the route of administration

- Single use container: add “Discard unused portion”

- Light sensitive product: consider the need for individual cartons
Suggestions/Reminders for the Manufacturer/Manufactured by Statement

- Include the place of business of the manufacturer, packer, or distributor. Refer to 21 CFR 201.1(i)

- For drug products manufactured in foreign countries, include the country of origin on the label. Refer to 19 CFR 134.11

- If the distributor is named on the label, include one of the qualifying phrases. Refer to 21 CFR 201.1(h)(5)

Manufactured by: Glenmark Generics Ltd.
Colvale-Bardez, Goa 403513, India.
GO/DRUGS/648

Manufactured for: Glenmark Generics Inc., USA
Mahwah, NJ 07430
Suggestions/Reminders for Child-Resistant Packaging

- The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging).

- If the unit-dose package carton is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be in a child-resistant container. 
  
  *Statement example: This unit-dose package is not child resistant.*
Suggestions/Reminders for Medication Guides

- Label statement should instruct the dispenser to provide a Medication Guide to each patient and should state how the Medication Guide it is provided. Refer 21 CFR 208.24
  - "PHARMACIST: Dispense the accompanying Medication Guide to each patient."
  - "PHARMACIST: Dispense the Medication Guide provided separately to each patient."

- Stand-alone Medication Guide
  - Type size no smaller than 10 points. Refer to 21 CFR 208.20
  - Provide sufficient numbers to distributors, packers, or authorized dispensers. Refer to 21 CFR 208.24
  - Include the statement: “Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.”

- Examples:
  - "PHARMACIST: Dispense the accompanying Medication Guide to each patient."
  - "PHARMACIST: Dispense the Medication Guide provided separately to each patient."

- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- How should I store temazepam?
  - Store temazepam at room temperature, 68°F to 77°F (20°C to 25°C).
Suggestions/Reminders for Physician Insert

GENERAL COMMENTS:
- Base your labeling on the most recently approved RLD labeling (check Drugs@FDA)
- After the patent/exclusivity expires, text that was previously protected should be put back in the labeling

DESCRIPTION section:
- Include the drug release test number if required by the USP monograph
- Include “USP dissolution test pending” for extended-release products waiting assignment of a test number

PKa section:
- Do not use proprietary names in sections describing clinical studies!!! This also refers to distributor labeling.
- When referring to your product in clinical studies, especially with ER products, generalize the study by using an article (e.g., In a study with...
Suggestions/Reminders for Physician Labeling

Use the same “Initial US Approval” year as the RLD

Should be the same as the RLD

Note: Do not include “Rx only” statement

Headings in the Highlights section:
- Center of a horizontal line
- Bold type
- Upper case

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN

Ambien® (zolpidem tartrate) tablets for oral administration

Initial US Approval: 1992

------------------------RECENT MAJOR CHANGES------------------------

Indications and Usage (1) 03/2007
Warnings and Precautions (5) 03/2007

------------------------INDICATIONS AND USAGE------------------------

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

------------------------DOSAGE AND ADMINISTRATION------------------------

- Adult dose: 10 mg immediately before bedtime (2.1)
- Elderly/Debilitated patients/Hepatic Impairment: Initial dose of 5 mg (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants (2.3)
- Total daily dose should not exceed 10 mg (2.4)
Suggestions/Reminders for Physician Labeling

The Agency recommends two-column format for Highlights and Contents sections.

Vertical line on the left edge
(for new or modified text listed under “Recent Major Changes”)

Solid Horizontal lines separate the sections

Minimum 6-point type for FDA-approved patient labeling that is not for distribution to patients