Current Trends in Labeling and Best Practices

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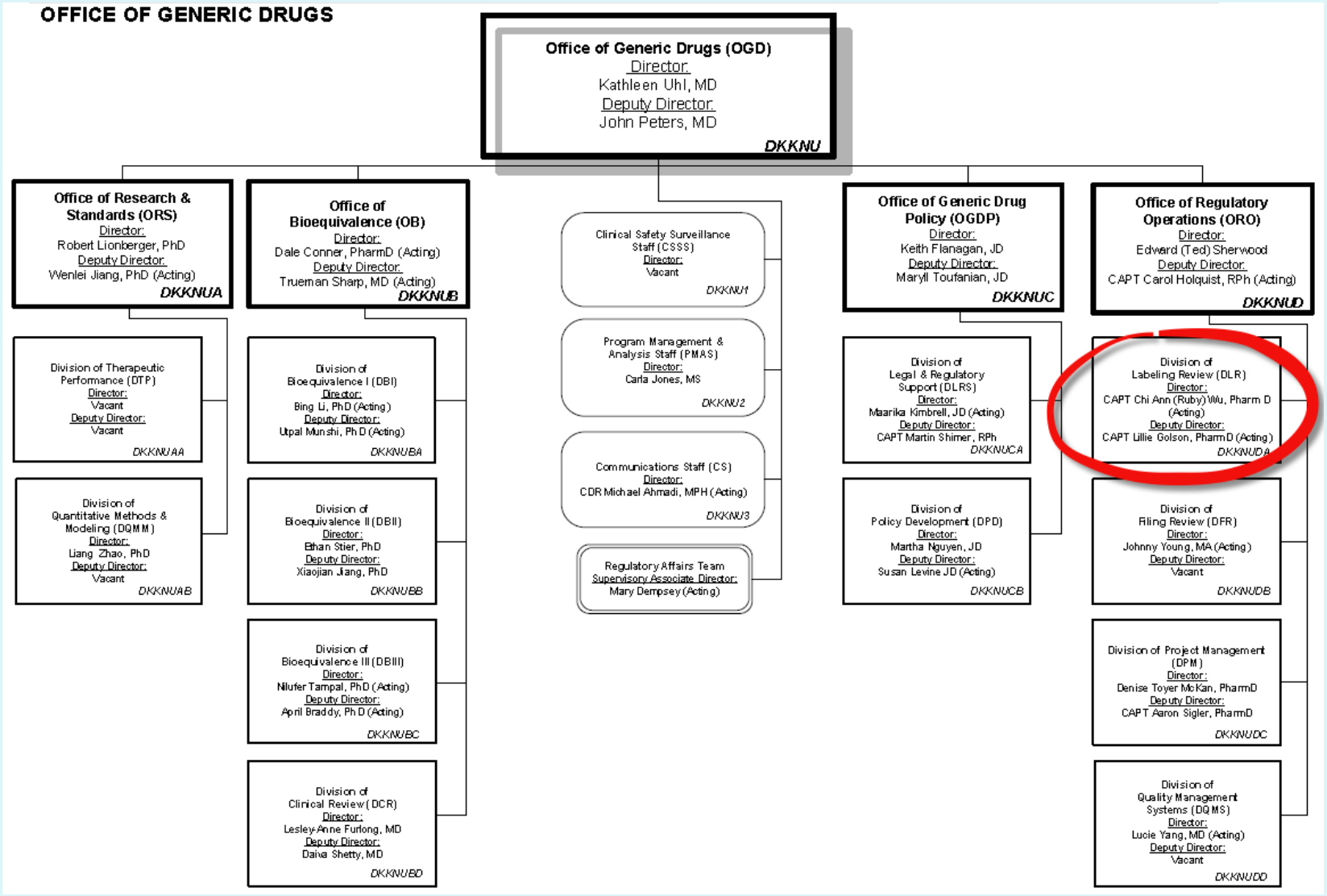
Food and Drug Administration/Office of Generic Drugs
CDER Small Business and Industry Assistance – Generic Drugs Forum
April 14, 2016

Objectives

- Provide an overview of the Division of Labeling Review (DLR)
- Provide DLR's recommendations on current trends and best practices to follow to ensure high quality labeling submissions
- Provide updates on recently published Guidances impacting labeling

Overview:
Division of Labeling Review
Office of Generic Drugs (OGD)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Increased Manpower

Staffing

Pre-GDUFA

- 16 Labeling Reviewers
- 3 Team Leaders
- 1 Project manager
- 3 Review Teams

Current

- 7 Review Teams
- 30 Labeling Reviewers
- 7 Team Leaders/Acting TLs
- 7 Project managers
- 4 Acting Supervisors
- 1 Technical Information Specialist
- 1 Support Staff


Focus

Steps DLR is taking to keep our GDUFA Commitments

- Reducing the number of review cycles
- Streamlining review efforts
- Aiming to ensure ANDA labeling remains consistent with the labeling of the reference listed drug (RLD)
- Working towards more consistency in labeling review recommendations across the division


12
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DLR's Recommendations:

Insert Labeling –

PLR Format

Insert labeling – PLR

- Highlights Title and Limitation Statement(HL)

Initial submission formatting

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use memantine hydrochloride tablets USP safely and effectively. See full prescribing information for memantine hydrochloride tablets USP.

MEMANTINE Hydrochloride Tablets USP, for oral use
Initial U.S. Approval: 2003

Preferred formatting of this section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MEMANTINE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information MEMANTINE HYDROCHLORIDE TABLETS.

MEMANTINE HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2003

Only the active ingredient, including the salt, should be in UPPER CASE

Drug Product name should be UPPER CASE: MEMANTINE HYDROCHLORIDE TABLETS

USP Descriptor should NOT appear in the HL section. May use in product quality sections (e.g., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING).

Product Title should only contain: Drug name, dosage form, route of administration, and controlled substance symbol

For more detailed information on PLR formatting, please refer to:
Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

Insert labeling – PLR (cont.)

- Recent Major Changes (201.57 (a)(5))
  - Removing a listing from Recent Major Changes
    - A changed section must be listed for at least 1 year after date of approval of the change
    - After 1 year, applicants can choose to:
      - Reprint labeling immediately to remove the listing or
      - Wait until the next reprinting to remove the listing
      - Report this change in an Annual Report

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

Insert labeling – PLR (cont.)

- **Adverse Reactions – Reporting contact information (201.57(a)(11))**
  - Include contact information for both the manufacturer and FDA. The completed statement should read:

    To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [manufacturer's phone number] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

  - Please note that **a phone number is required**. The addition of a web address of the direct link to a site dedicated to adverse reaction reporting may also be included. An email address or a link to the homepage of a company's website cannot be used.

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

Insert labeling – PLR (cont.)

- Omitted Sections (201.56(d)(4))
  - When omitted from Full Prescribing Information (FPI), the section or subsections must also be omitted from the Contents.
  - The heading "Full Prescribing Information: Contents* should be used and the statement: "*Sections or subsections omitted from the full prescribing information are not listed." must appear at the end of Contents (see example).
  - When there is an omission, subsequent sections and subsections should not be renumbered.
  - Tables and graphs, when carved out of the labeling, should also not be renumbered.

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013. Appendix E
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

Insert labeling – PLR (cont.)

- Type size Requirements for Labeling & FDA-approved Patient Labeling

	Type Size Requirements for Labeling	FDA-Approved Patient Labeling Included with Labeling	Type Size Requirements for FDA-Approved Patient Labeling
PLR Format (21 CFR 201.57)			
Trade Labeling (i.e., labeling on or within the package from which the drug is to be dispensed)	Minimum 6-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 6-point type
		Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients	Minimum 6-point type*
		Medication Guide that is for distribution to patients	Minimum 10-point type
Other Labeling (e.g., labeling accompanying promotional materials)	Minimum 8-point type	FDA-approved patient labeling that is not for distribution to patients	Minimum 8-point type
		Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients	Minimum 8-point type*
		Medication Guide that is for distribution to patients	Minimum 10-point type
Old Format (21 CFR 201.80)			
Trade Labeling and Other Labeling	No minimum requirement	FDA-approved patient labeling that is not for distribution to patients	No minimum requirement
		Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients	No minimum requirement*
		Medication Guide that is for distribution to patients	Minimum 10-point type

*FDA does not require, but encourages a minimum type size of 10 points for this information.

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013. Appendix D
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf

DLR's Recommendations:

Injectable Drug Products

Labeling for Injectable Drug Products

- Formatting of Expiration Dates
  - Expiration date is the time during which the drug product is expected to meet the compendial requirements, provided it is stored properly.
  - Received 4 Med Error Reports for the product below.
  - Practitioners could not understand the expiration date
  - DLR recommended the format found in the USP General Notices:

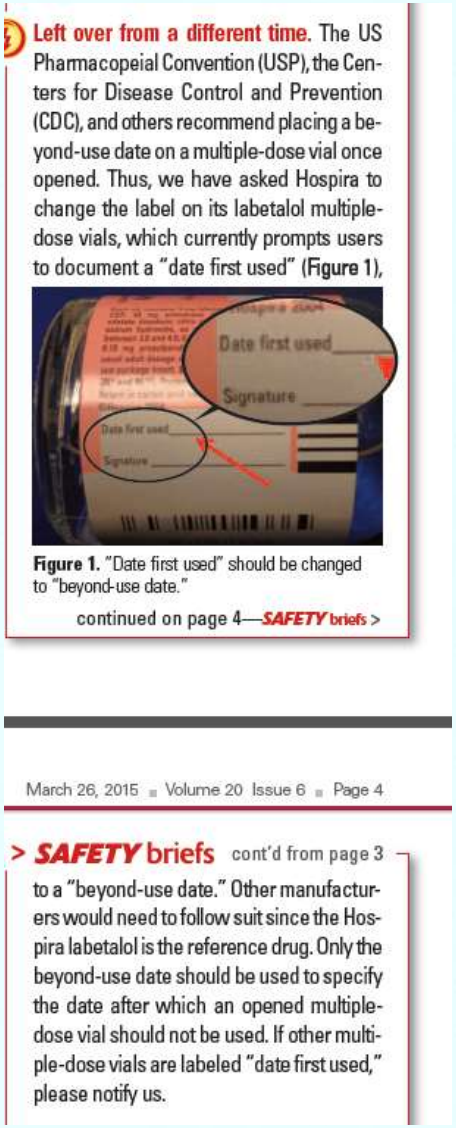
10.40.100. Expiration Date and Beyond-Use Date

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., “EXP 6/08,” “Exp. June 08,” or “Expires 6/08”).

Labeling for Injectable Drug Products (cont.)

- Formatting of Beyond-Use Date (BUD)
  - Beyond-use date is the last date a drug can be used and shall be no later than the manufacturer's expiration date.
  - An ISMP article generated med error reports
  - After consultation with the Division of Medication Error Prevention and Analysis (DMEPA), the Agency recommends that the following format be used to comply with the BUD requirement:

    Discard after __/__/__



Left over from a different time. The US Pharmacopeial Convention (USP), the Centers for Disease Control and Prevention (CDC), and others recommend placing a beyond-use date on a multiple-dose vial once opened. Thus, we have asked Hospira to change the label on its labetalol multiple-dose vials, which currently prompts users to document a "date first used" (**Figure 1**),

Figure 1. "Date first used" should be changed to "beyond-use date."

continued on page 4—*SAFETY* briefs >

March 26, 2015 ■ Volume 20 Issue 6 ■ Page 4

> ***SAFETY*** **briefs** cont'd from page 3

to a "beyond-use date." Other manufacturers would need to follow suit since the Hospira labetalol is the reference drug. Only the beyond-use date should be used to specify the date after which an opened multiple-dose vial should not be used. If other multiple-dose vials are labeled "date first used," please notify us.

Labeling for Injectable Drug Products (cont.)

- **Being the 'same as' regarding package size**
  - For injectable products, if the RLD for your product is a single-dose, your product should also be single-dose.
  - You can only claim multiple-dose if your RLD comes packaged that way as well.
- **2-port IV bags**
  - Complaints have come in regarding 2-port IV bags.
  - Concerned that having an additive port that is not needed might encourage adding a drug, thus causing potential incompatibility issues.
  - Please take these concerns into consideration when packaging your IV product.

Labeling for Injectable Drug Products (cont.)

- Expression of strength of Local Anesthetics (e.g., lidocaine)
  - Include 3 expressions:
    - Percent
    - Total drug/total volume
    - mg/mL

1% (100 mg/10 mL) **OR** **1%**
(10 mg/mL) **100 mg/10 mL**
(10 mg/mL)

Additional Recommendations

Miscellaneous

Additional Recommendations

- Logo Location
  - To reduce clutter and enhance readability of important information on the principal display panel (PDP), you are asked to place your company logo on the side, back panel, or lower portion of the PDP.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Additional Recommendations (cont.)

- **The Reference Listed Drug (RLD) for Abbreviated New Drug Application (ANDA) Labeling**
  - The NDA RLD should be used for labeling comparisons, even if discontinued.
    - When the NDA RLD is discontinued, FDA may designate an ANDA as the reference product in the Orange Book. Applicants seeking approval of an ANDA that relies upon the withdrawn NDA RLD should use this reference product for conducting BE testing, but the NDA RLD should continue to be used for labeling comparisons.
  - Efforts are made to have discontinued NDAs update their labeling.
    - Enables ALL ANDAs to update labeling immediately.
    - Allows for more extensive revisions, if warranted.

Additional Recommendations (cont.)

- **Safety Labeling Changes for discontinued products**
  - Under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act, FDA can require safety-related labeling changes for NDAs, BLAs, and ANDAs under certain circumstances.
  - This authority applies to both marketed products *and* to products that are *not marketed* (e.g., discontinued), unless approval of the product has been withdrawn in a Federal Register notice.
  - Therefore, DLR asks that when letters are sent requesting labeling updates, you promptly comply rather than emailing asking for an exemption because you are *not marketing the product*.
    - This will save DLR a lot of time in responding "no" with an explanation to you, or in having to contact you repeatedly for not responding in the requested timeframe.
    - Prompt compliance should be easier now that labeling can be submitted in draft.

Additional Recommendations (cont.)

- **Side-by-side comparisons**
  - When revising your labeling due to updated RLD labeling, provide a comparison of your proposed labeling to the RLD labeling.
  - When revising your labeling to address deficiencies identified by the Agency, provide a comparison of your proposed labeling to your last approved labeling.

Additional Recommendations (cont.)

- **Hyphenated or Compound Words**
  - DLR requests that you use lower case for the 2nd portion of hyphenated words unless part of a title.

    In a title on a label: Doxycycline Extended-Release Capsules

    In a sentence in a letter: Doxycycline Extended-release Capsules
  - Other common hyphenated terms:
    - delayed-release
    - unit-dose
    - unit-of-use
    - multiple-dose
    - single-dose

Additional Recommendations (cont.)

- **Distributor Labeling**
  - Please be reminded that you, the ANDA holder, are the *Owner* of the drug product and thus ultimately responsible for the labeling of those you contract with (e.g., your distributors.)
  - Distributor and repacker labeling on The DailyMed website oftentimes is inconsistent with labeling approved for the ANDA.
  - Ensure that the name of only one distributor appears on the label/labeling.
  - Make certain your labeling and that of your distributors are updated on The DailyMed website.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf

Additional Recommendations (cont.)

- **Submitting same labeling change to both an NDA and ANDA that references the NDA**
  - Most efficient and cost effective approach:
    - First, submit labeling change for the NDA product ONLY.
    - After the labeling change(s) is approved for the NDA product, then submit a conforming CBE supplement for the ANDA product that references that NDA.

Additional Recommendations (cont.)

- **Title case lettering**
  - Use title case lettering rather than all uppercase lettering for the established name on container labels, carton labeling, and blisters. Title case lettering enhances readability (e.g., Drugozide Injection rather than DRUGOZIDE INJECTION)

Title case preferred

Additional Recommendations (cont.)

- **Tall Man Lettering**
  - Working with DMEPA to update entries on FDA's website
  - Please contact DLR before adding tall man lettering to products not currently appearing on the list
  - In the interim, note the following change:

Nifedipine	NiCARdipine NIFEdipine
Prednisone Prednisolone	PredniSONE PrednisoLONE
Risperidone Ropinirole	risperiDONE rOPINIRole

Preferred presentation:
Begin Tall Man word with lower case letter rather than UPPER-CASE unless its part of the tall man lettering like NIFEdipine.

Additional Recommendations (cont.)

- **Deletion of terminal zeros**
  - From USP General Notices

    10. Preservation, Packaging, Storage, and Labeling
    10.40.20. Use of Leading and Terminal Zeros
    To help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than 1 shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).
  - Therefore, terminal zeros are objectionable only when referring to dosage or strength. Delete them only when used in that context (e.g., D&A), not throughout your labeling (e.g., blood levels, statistical values, etc.) unless the NDA RLD has deleted them.

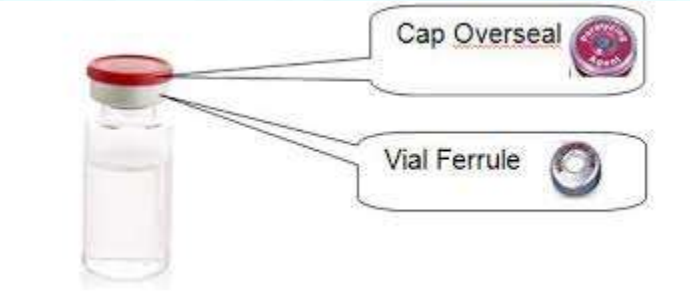
Additional Recommendations (cont.)

- **USP drug products**
  - Only use USP with the established name in the product quality sections of the insert labeling (e.g., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING). Please do not use throughout the insert or in the HL section.

Gentle Reminder's

Gentle Reminders

- **Labeling on Cap/Ferrule Overseal (USP GC <1> and <7>)**
  - **Effective Dec. 1, 2013**, only cautionary statements, statements intended to prevent imminent, life-threatening situations, may appear on the top surface of the ferrule and/or cap overseal of a vial.
  - The statement should appear on both the ferrule and cap, unless the cap overseal is transparent and the statement is legible.
  - If no cautionary statement is necessary, top surface should remain blank.
  - State whether or not text appears on your ferrule/cap overseal in 3.2.P.7 of Module 3 of your submission.
  - **Inappropriate statements (e.g., flip-off) must be removed prior to approval.**



http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

Gentle Reminders (cont.)

- For drug products manufactured in a foreign country, include the country of origin on the label/labeling.
- When submitting labeling in pdf format, submit text-based, not a scanned version to enable use of the search and compare functions.
- Please ensure that all versions of your insert labeling are consistent (e.g., draft and SPL). Oftentimes there are discrepancies.
- If proposing to change the trade dress for your entire product line, please contact DLR for guidance. Such a change might require submission of a PAS.

Gentle Reminders (cont.)

- Refrain from making unsolicited changes to your labeling…especially right before approval. Inadvertent mistakes are often made requiring correction before application can be approved.
- Before submitting labeling amendments, please, please, please check Drugs@FDA for RLD updates. Not submitting the most up-to-date labeling results in an automatic deficiency!
- For REMS submissions, please do not submit labeling unless specifically requested to do so.

Gentle Reminders (cont.)

- When submitting supplements for manufacturing site changes, please do not submit labeling for this change UNLESS it involves a change in the appearance of the container label/carton labeling. A site change only impacting the insert labeling may be made in an Annual Report.
- Please do not include the name of more than one distributor on the same label.

Express unit-dose cups as strength per total volume

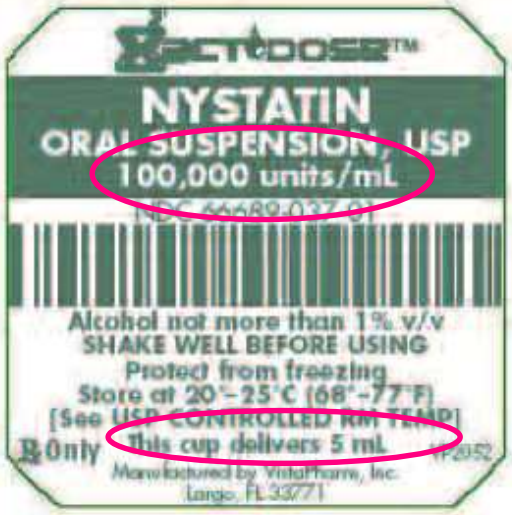


Figure 1. This nystatin 100,000 units/mL container holds 5 mL, which is often missed.

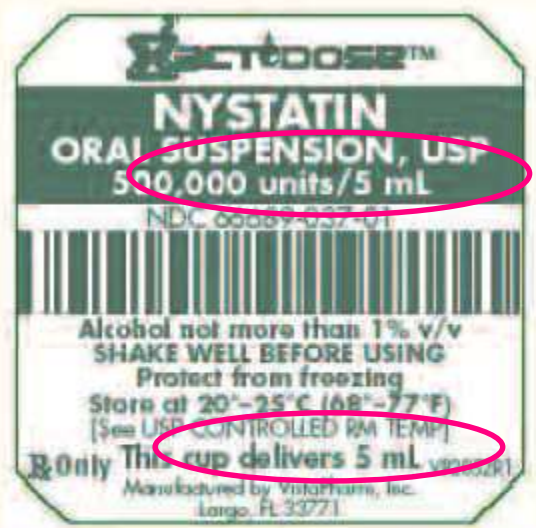
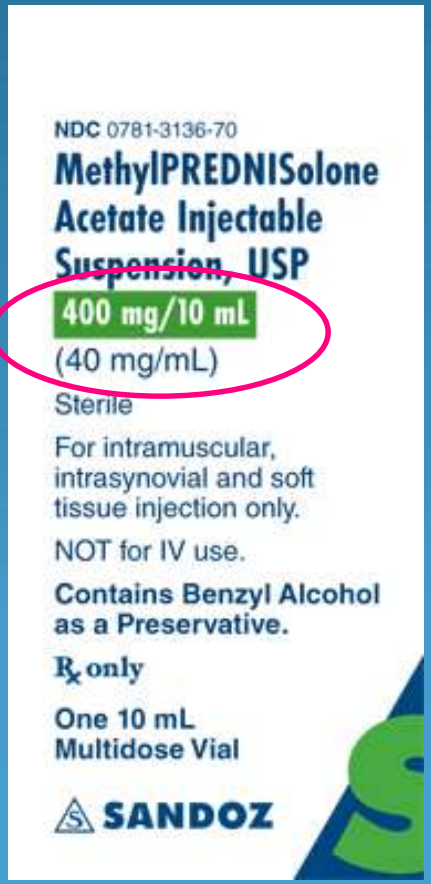


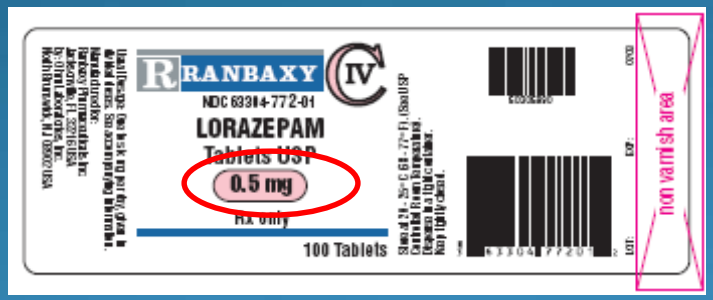
Figure 2. Label revision now clearly states 500,000 units/5 mL.

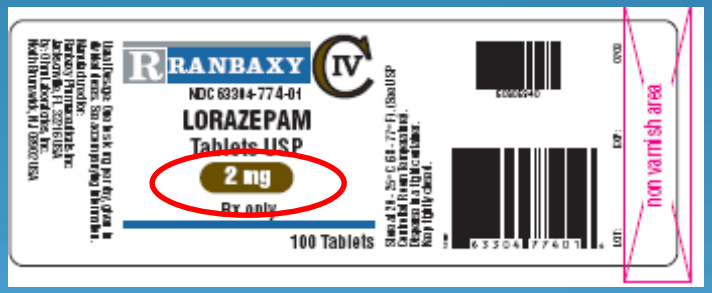
From ISMP Report 12/02/2010

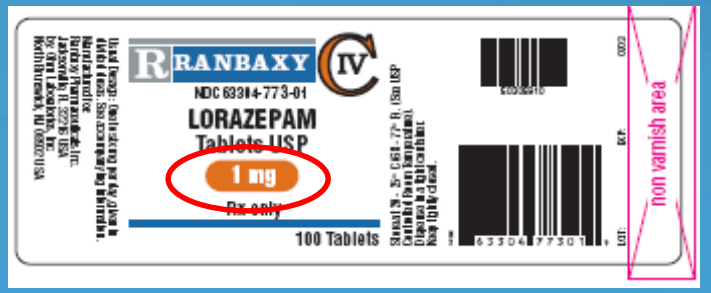
Express injection products as strength per total volume followed in close proximity by strength per mL



Differentiate product strengths by boxing, color, or other means







Gentle Reminders (cont.)

- Ensure that 356(h) form is up-to-date.
- Report any POC changes as soon as possible, especially email address changes.
- For labeling questions, please contact the Regulatory Project Manager (RPM) for your product.

News Flash!

Draft Labeling Acceptable for Approval in OGD

- **A guidance for industry titled: *Acceptability of Draft Labeling to Support ANDA Approval* issued early October, 2015**
  - Provides for the labeling content of ANDAs to be approved in draft as long as any outstanding labeling deficiencies are minor and editorial in nature.
  - Carton and container labeling should present an accurate representation of the layout, text size and style, color, and other formatting factors that will be used with the Final Printed Labeling (FPL).
  - Applicant holders must ensure that content of the FPL is identical to the approved labeling. Not doing so might render the drug product misbranded and an unapproved new drug.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM465628.pdf

Recommendations for Labeling with Appropriate Package Type Terms for Injectable Drug Products for Human Use Draft Guidance published October 2015

Old Package Type Terms	New Package Type Terms
Single-dose/single-use	Single-dose (only)
Multiple-dose/multiple-use	Multiple-dose (only)
	Single-patient-Use

- FDA recommends that terms appear on all labeling components.
- Include a discard statement on single-dose & single-patient-use products.
- Make labeling changes within 2 years of publication of final guidance
- Clearly identify supplement on the cover letter with “Labeling Changes to Follow the Package Type Term Guidance.”
- A change from “single-use” to “single-dose” may be annual reportable.
- For all other changes, please refer to the Guidance.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

New USP General Chapter <7>: Labeling

- Becomes official May 1, 2016
- All information pertaining to labeling moved from other chapters to Chapter <7>
- Until it becomes official, labeling information can still be found in current chapters

Summary

- Provided overview of OGD/DLR
- Shared DLR's recommendations on current trends and best practices to follow to submit quality reviews
- Provided overview of recently issued FDA Guidances that impact labeling

Thank You!

surveymonkey.com/r/GDF-D2S4