ANDA Labeling: Helpful Hints and Resources

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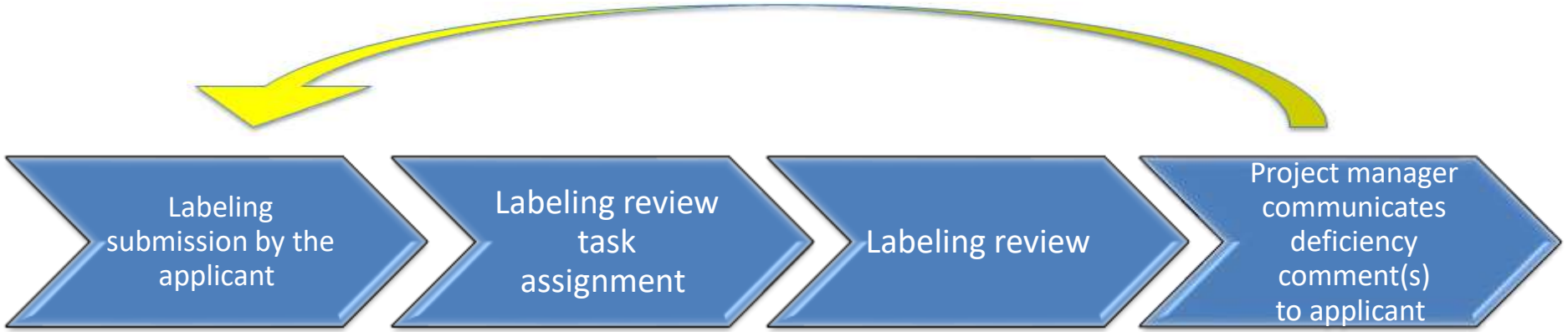
Objectives

- Provide general overview of the Abbreviated New Drug Application (ANDA) labeling review process.
- Provide helpful hints and resources to use for quality labeling submissions.

Division of Labeling Review (DLR)

Review Process Overview



Division of Labeling Review (DLR)

Review Process Overview

Review focus:

- Ensure that the generic labeling is the “same as” the approved labeling for the product’s reference listed drug (RLD), **except for differences allowed** under
  - Section 505(j)(2)(A)(v) of the Act
  - 21 CFR 314.94(a)(8)
- Ensure that the labels and labeling accurately reflect the drug product information and provide sufficient information for safe use of the product

Division of Labeling Review (DLR)

Review Process Overview

Labeling components reviewed:

- Container Labels and Carton Labeling
- Prescribing Information (Rx)
- Drug Facts Labeling (Over-the-Counter)
- Medication Guide
- Patient Information Leaflet
- Instructions for Use

Helpful Hints and Resources

Labeling Components

- ❑ Prescribing Information
- ❑ Medication Guide
- ❑ Instructions for Use and Patient Information
- ❑ Container/Carton Labeling

Product Specific

- ❑ Injectable products
- ❑ Ophthalmic products
- ❑ Over-the-counter (OTC)
- ❑ Controlled Substances
- ❑ Imprints
- ❑ Inactive Ingredients
- ❑ Color Coding
- ❑ Tall Man Lettering

Other helpful references

Prescribing Information

Format

- We recommend that both Microsoft Word document and PDF text versions be submitted for Prescribing Information and Patient Labeling pieces.
  - *Refer to ANDA Submissions-Content and Format Guidance for Industry* *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-content-and-format-abbreviated-new-drug-application*
- The information between the two versions should be consistent.

Prescribing Information

Format Discrepancies

Microsoft Word Document

13 NONCLINICAL TOXICOLOGY

14 Carcinogenesis, Mutagenesis, Impairment of Fertility

15 CLINICAL STUDIES14.1 Adjunctive Treatment of Major Depressive Disorder

PDF Text Document

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis,

Impairment of Fertility

14 CLINICAL STUDIES

14.1 Adjunctive Treatment of Major Depressive Disorder

Prescribing Information

Editorial Revisions

Revisions

Conduct editorial revisions throughout Prescribing Information and Patient Package Information (e.g., Medication Guide, Patient Information, Instructions for Use) for spelling, spacing, typographical, grammatical, or data errors.

Examples of editorial errors

- Spacing error:

  “should be alertedabout”

  “should be alerted about”
- Duplicate text

  “should be alerted about should be alerted about”
- Spelling

  "shod bee alerted about"

Prescribing Information

Physician Labeling Rule (PLR)

For PLR format for the Prescribing Information

- *Refer to 21 CFR 201.57(d)*

Ensure the FDA Toll Free Number, MedWatch web address, and manufacturer's phone number are present in the labeling.

- *Refer to 21 CFR 201.57(a)(11)(ii)*

Medication Guide

Provide a statement that a sufficient number of Medication Guides are available for dispensing and distribution for your drug product.

- *Refer to 21 CFR 208.24(b)*

"Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients…"

Medication Guide

Electronic MG

It is acceptable for a generic applicant to offer the Medication Guide electronically by including a URL in their labeling even if the reference listed drug (RLD) does not take this approach. A manufacturer providing the means to produce Medication Guides through a website remains responsible for fulfilling its obligations under 21 CFR 208.24(b)(2), including ensuring that the referenced links are correctly listed and are operational.

Changes Being Effected (CBE-0) supplement may be submitted for this change.

Medication Guide

Electronic MG – continued

Website Display

An applicant may use an informational statement and non-promotional website to instruct the authorized dispenser to access a website and print a copy of the Medication Guide to provide to each patient to whom the drug product is dispensed. Based on current technology, the website should display a PDF version of the Medication Guide.

We suggest: “ www.companyname/medguide/drugname.pdf ”

Medication Guide

Electronic MG – Continued

Statement in PI and MG

We recommend adding a statement to the end of the Prescribing Information (PI) and to the top of the Medication Guide (MG) to alert dispensers that a Medication Guide will need to be printed.

We suggest: "Dispense with Medication Guide available at: www.companyname/medguide/drugname.pdf"

Medication Guide

Electronic MG – Continued

Statement on Container/Carton

We also recommend adding a statement to the packaging (immediate container label and carton), subject to spacing limitations, which identifies the link to the electronic Medication Guide.

We suggest: "Print Medication Guides at:

www.companyname/medguide/drugname.pdf"

Instructions for Use and Patient Information Leaflet

If the instructions differ from the RLD, explain the reason for the differences in a side-by-side comparison in accordance with 21 CFR 314.94(a)(8)(iv) and provide information related to similar instructions approved for another of your approved drug products, if available.

Container/Carton Labeling

Lot Number

A lot number, control number, or batch number must appear on the label.

- *Refer to 21 CFR 201.18*

Container/Carton Labeling

Expiration Date

The following four formats are recommended for the expiration date.

- If only numerical characters are used:

  YYYY-MM-DD

  YYYY-MM (if space is limited)

- If alphabetical characters are used to represent the month

  YYYY-MMM-DD

  YYYY-MMM (if space is limited)

➢ *Refer to the FDA's guidance for industry, Product Identifiers under the Drug Supply Chain Security Act Questions and Answers and the USP General Chapter <7> Labeling (Not Yet Official, effective 2023).*

Container/Carton Labeling

Bar Code

Ensure the linear bar code contains the National Drug Code (NDC) and is surrounded by sufficient blank space so that the bar code can be scanned correctly.

- *Refer to 21 CFR 201.25(c)(i)*

Container/Carton Labeling

Bar Code

We encourage you to orient the bar code to appear vertically, as the curvature of the container (e.g., small vials, ampules, prefilled syringes) may distort the linear bar code and negatively impact scanning.

- *Refer to the FDA's guidance for industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*

Container/Carton Labeling

Format and Examples

Formatting and Wording Preferences

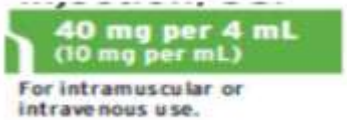
Ensure the established name, expression of strength, and route of administration (if it is not for oral use) are prominently presented on the label.

- *Refer to 21 CFR 201.15, 21 CFR 201.50, and 21 CFR 201.100*

Examples:

- Mydrug Tablets

- Mydrug Injection



Container/Carton Labeling

Strength Differentiation

Strength Differentiation

- Ensure your container/carton labeling for different strengths are sufficiently differentiated to reduce chance of medication errors.

- We recommend you also consider other pending ANDAs and approved products to ensure adequate differentiation of similar products (e.g., immediate-release versus extended-release formulations).

Guidance and Example

- Refer to the *FDA's guidance for industry, Safety Considerations for Container and Carton Labeling Design to Minimize Medication Errors for more information.*

- **Example:**

Helpful Hints and Resources

Labeling Components

- ❑ Prescribing Information
- ❑ Medication Guide
- ❑ Instructions for Use and Patient Information
- ❑ Carton/Container Label

Product Specific

- ❑ Injectable products
- ❑ Ophthalmic products
- ❑ Over-the-counter (OTC)
- ❑ Controlled Substances
- ❑ Imprints
- ❑ Inactive Ingredients
- ❑ Color Coding
- ❑ Tall Man Lettering

Other helpful references

Injectable Products

Expression of Strength

Dry powder injectable products

Express in terms of the quantity of drug per vial

XX mg/vial

1 gram / vial

500 mg/vial

or

XX mg per vial

500 mg per vial

- *Refer to the FDA's guidance for industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*

Injectable Products

Expression of Strength

Small volume parenteral products

Express total quantity per total volume followed by the concentration per milliliter (mL)

Examples: 100 mg/5 mL (20 mg/ml)

- *Refer to USP General Chapter <7> Labeling and FDA's guidance for industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*

Injectable Products

Single-Dose Products

Include a discard statement on the container label and other labeling as appropriate and as space permits

Example statement: **“Discard unused portion.”**

- *Refer to FDA’s guidance for industry, Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.*

Injectable Products

Pharmacy Bulk Packages

Add a prominent, boxed declaration reading **“Pharmacy Bulk Package – Not for Direct Infusion”** on the principal display panel following the expression of strength.

- *Refer to USP General Chapter <7> Labeling and FDA’s guidance for industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*

Injectable Products

Ferrule and cap overseal

Ferrule and cap overseal should be blank unless you have a critical cautionary statement.

Injectable Products

Ferrule and cap overseal

Neuromuscular blocking agent or paralyzing agents:

- Must meet the labeling requirements set forth in the USP General Chapter <7> Labeling

Injectable Products

Aluminum Contents

Aluminum content labeling requirements for parenterals used in total parenteral nutrition (TPN)

- *Refer to 21 CFR 201.323*

Injectable Products

Warning Statement for Rubber

For container/closure containing rubber, include the following warning statement in bold print on the principal display panel:

"Caution: This Product Contains Natural Rubber Latex Which May Cause Allergic Reactions."

- *Refer to 21 CFR 801.437*

Ophthalmic Products

Limit color coding to the cap color

- *FDA's guidance for industry, Safety Considerations for Container and Carton Labeling Design to Minimize Medication Errors*
- *The Academy of Ophthalmology (AAO) for uniform color coding of caps for ophthalmic drug products based on the pharmacological category*

Over-the-Counter (OTC)

Labeling Requirements

- Refer to 21 CFR 201

§ 201.60 - Principal display panel
§ 201.61 - Statement of identity
§ 201.62 - Declaration of net quantity of contents
§ 201.63 - Pregnancy/breast-feeding warning
§ 201.64 - Sodium labeling
§ 201.66 - Format and content requirements
§ 201.70 - Calcium labeling
§ 201.71 - Magnesium labeling
§ 201.72 - Potassium labeling
§ 201.80 - Specific requirements on content and format of labeling

Packaging Requirements

- Refer to 21 CFR 211.132 for tamper-evident packaging requirements

Over-the-Counter (OTC)

Drug Facts Labeling format requirements

- Refer to 21 CFR 201.66
- Ensure to include a Labeling Format Information Table (legend) that details the formatting with your submission

Example of Legend

(Label represents actual size)
Labeling Format Information

Fonts:	Helvetica Neue LT Standard
Drug Facts:	10 pt
Header:	8 pt
Subheader:	6 pt
Body Text:	6 pt
Drug Facts (cont.):	9 pt
Bullets:	6 pt
Barlines:	2.5 pt
Hairlines:	.5 pt

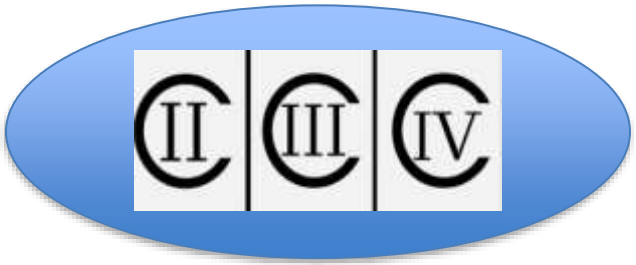
Controlled Substances

Packaging requirements for tamper-evident sealing

- *Refer to 21 CFR 1302.06*

Regulatory requirements for location and size of symbol

- *Refer to 21 CFR 1302.04*



Solid Oral Dosage Form

Imprint Requirement

MUST conform to imprint requirements set forth in 21 CFR 206.10

Inactive Ingredients

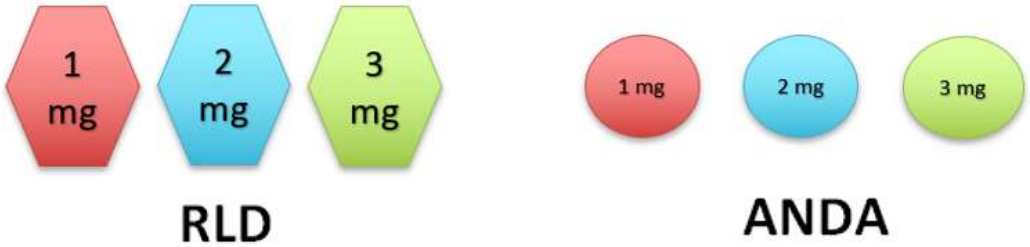
Special labeling statements and regulatory requirements:
(Note: below is not an exhaustive list)

- FD&C Yellow No. #5 (tartrazine)
- Yellow #6
- Aspartame
- Sulfite

➢ *Refer to 21 CFR 201.20, 21 CFR 201.21, and 21 CFR 201.22*

Color Coding

For products that are expected to have the same color as the reference listed drug, refer to the “Color Coding” section of the FDA’s guidance for industry, *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.



Tall Man Lettering

Refer to the FDA Name Differentiation Project webpage for a list of products recommended to use Tall Man Lettering.

Established Name	Recommended Name
Acetohexamide Acetazolamide	acetoHEXAMIDE acetaZOLAMIDE
Nicardipine Nifedipine	niCARdipine NIFEdipine

Additional Helpful References

FDA's Prescription Drug Labeling Resources

https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling resources#Generic%20Drug 20Products%20-Specific%20Labeling%20Resources

USP Resources www.uspnf.com

- USP General Chapter <7> Labeling
- USP General Chapter <659> Packaging and Storage Requirements
- USP General Chapter <1121> Nomenclature
- USP General Chapter <1151> Pharmaceutical Dosage Forms

Additional Helpful References

FDA Guidance for Industry

- Updating ANDA Labeling After the Marketing Application for the RLD Has been Withdrawn (draft guidance)
- Good ANDA Submission Practices (draft guidance)
- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (draft guidance)
- Safety Considerations for Product Design to Minimize Medication Errors (final guidance)
- Child-Resistant Packaging Statements in Drug Product Labeling (final guidance)

Additional Helpful References

FDA Guidance for Industry – continued

- Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (final guidance)
- Acceptability of Draft Labeling to Support ANDA Approval (draft guidance)
- Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers (draft guidance)
- Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (final guidance)
- Changes to an Approved NDA or ANDA (final guidance)

Challenge Question

Can the Medication Guide be provided electronically?

A. YES

B. NO

Challenge Question

Which drug products require a tamper-evident packaging requirement?

A. Controlled Substance Drug Products
B. OTC Drug Products
C. Non-Controlled Substance Drug Products
D. Both A & B


Thank You!

Questions?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