COMMON LABELING ISSUES AND GENERAL TIPS FOR ABBREVIATED NEW DRUG APPLICATIONS (ANDAS)

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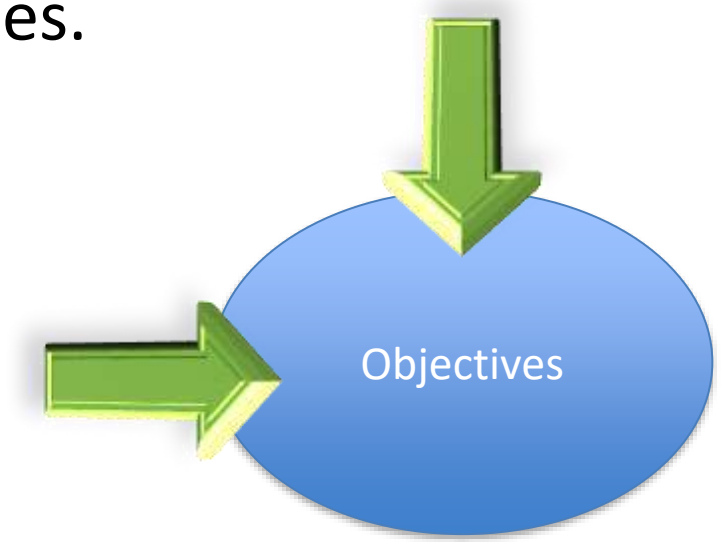
OBJECTIVES

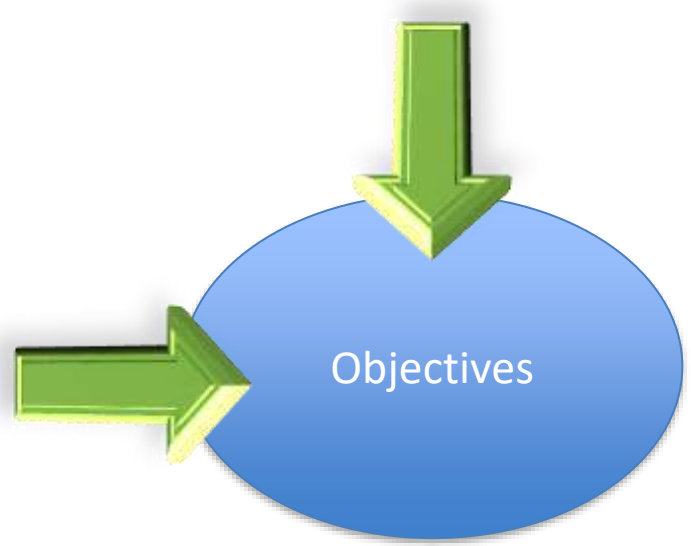
- This presentation will address common issues regarding ANDA labeling along with discussing topics to ensure high-quality labeling submissions which will potentially reduce review cycles.

- This discussion will increase knowledge on ANDA labeling related topics and assist applicants with providing high-quality labeling submissions and potentially reduce review cycles.



OBJECTIVES (CONT.)

- Provide overview of the following:
  - General Information for ANDA Labeling
  - Medication Guide Requirements
  - USP Monographs
  - Different Package Type Terms
  - Impact of Patents and Exclusivities
  - Over-the-counter (OTC) Products
  - Different Types of Supplements



GENERAL INFORMATION FOR ANDA LABELING

Labeling Updates for Non-marketing ANDAs

- Even if an ANDA is not marketing, the applicant must submit updated labeling to be the same as the most recently approved reference listed drug (RLD) label per CFR 201.56(a)(2)
- In the event the RLD label is withdrawn, refer to the FDA guidance, *Updating ANDA Labeling after the Marketing Application for the Reference Listed Drug has been Withdrawn*
  - "…ANDAs that are pending or generic drugs that continue to be marketed under one or more ANDAs that rely on the withdrawn RLD, the labeling of those pending or marketed ANDA products may need to be updated to reflect changes that would have been necessary had the New Drug Application (NDA) for the RLD not been withdrawn."

GENERAL INFORMATION FOR ANDA LABELING (CONT.)

Format for labeling submissions

- The Prescribing Information (PI) should be in both PDF text and Word Documents
  - Ensure the documents submitted are the same as the latest RLD labeling found at Drugs@FDA

    https://www.accessdata.fda.gov/scripts/cder/daf/
  - Ensure labeling provided is in PDF text and Word Documents. Both documents should be consistent between themselves

GENERAL INFORMATION FOR ANDA LABELING (CONT.)

PDF Text

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis,

Impairment of Fertility

14 CLINICAL STUDIES

14.1 Adjunctive Treatment of Major Depressive Disorder

Word Document

13 NONCLINICAL TOXICOLOGY

14 Carcinogenesis, Mutagenesis, Impairment of Fertility

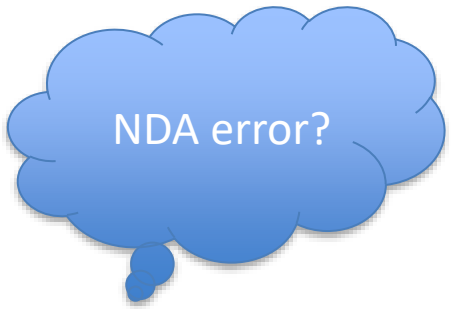
15 CLINICAL STUDIES14.1 Adjunctive Treatment of Major Depressive Disorder

Important to recognize that this is a simple error, but more complex errors occur between the documents, including the Final Printed Labeling (FPL), if one is submitted.

GENERAL INFORMATION FOR ANDA LABELING (CONT.)

Handling Errors in New Drug Application (NDA) Labeling

- In general, ANDA should follow the NDA RLD, even if NDA is wrong. If the error is for information that has safety concerns, please raise this issue to the regulatory project manager (RPM) if it pertains to your ANDA or DrugInfo@fda.hhs.gov if it pertains to a general question



GENERAL INFORMATION FOR ANDA LABELING (CONT.)

NDA Label Error Examples

- CONTENTS*/6 ADVERSE REACTIONS: 6.1 Clinical Studies Experience
- CONTENTS*:1.2 Opioid-Induced Constipation

ANDA Label Submission

- CONTENTS*/6 ADVERSE REACTIONS: 6.1 Clinical Trials Experience
- CONTENTS*:1.2 Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

GENERAL INFORMATION FOR ANDA LABELING (CONT.)

Manufacturing Statements and Format

- Please include one of the qualifying statements found in 21 CFR 201.1(h)(5) or (6) on the drug product labels and labeling
- Also, include a statement of the place of business per 21 CFR 201.1(i)
  - Please make sure this information is consistent across all labeling pieces where it is listed/required
  - Example:

Manufactured for: Drugs, Inc.
Silver Spring, MD 20903

GENERAL INFORMATION FOR ANDA LABELING (CONT.)

Q1/Q2 Parenteral Products

- Q1/Q2 parenteral ANDA labeling should be the same as the RLD and include all sections (e.g., “2.6 Compatibility With Other Antiepileptic Drugs” which is found in the RLD labeling)
- ANDA’s should be the same as the RLD with Q1/Q2 products because the active and inactive ingredients are the same with the exceptions of preservatives, buffer substances to adjust tonicity, or thickening agents. Refer to 21 CFR 314.94 (a)(9)(iv)

MEDICATION GUIDES

Appropriate Medication Guide Statements

- Pharmacist:

  "Dispense the enclosed Medication Guide to each patient." or

  "Dispense the accompanying Medication Guide to each patient." or

  "Dispense the Medication Guide provided separately to each patient."

An appropriate Medication Guide statement should be in a prominent and conspicuous manner, as required per 21 CFR 208.24(d).

MEDICATION GUIDES (CONT.)

Medication Guide Availability Online

- It is acceptable for a generic applicant to offer the Medication Guide electronically by including an URL in their labeling even if the 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
- This type of change may be submitted as a changes being effected 0 (CBE-0) supplement

MEDICATION GUIDES (CONT.)

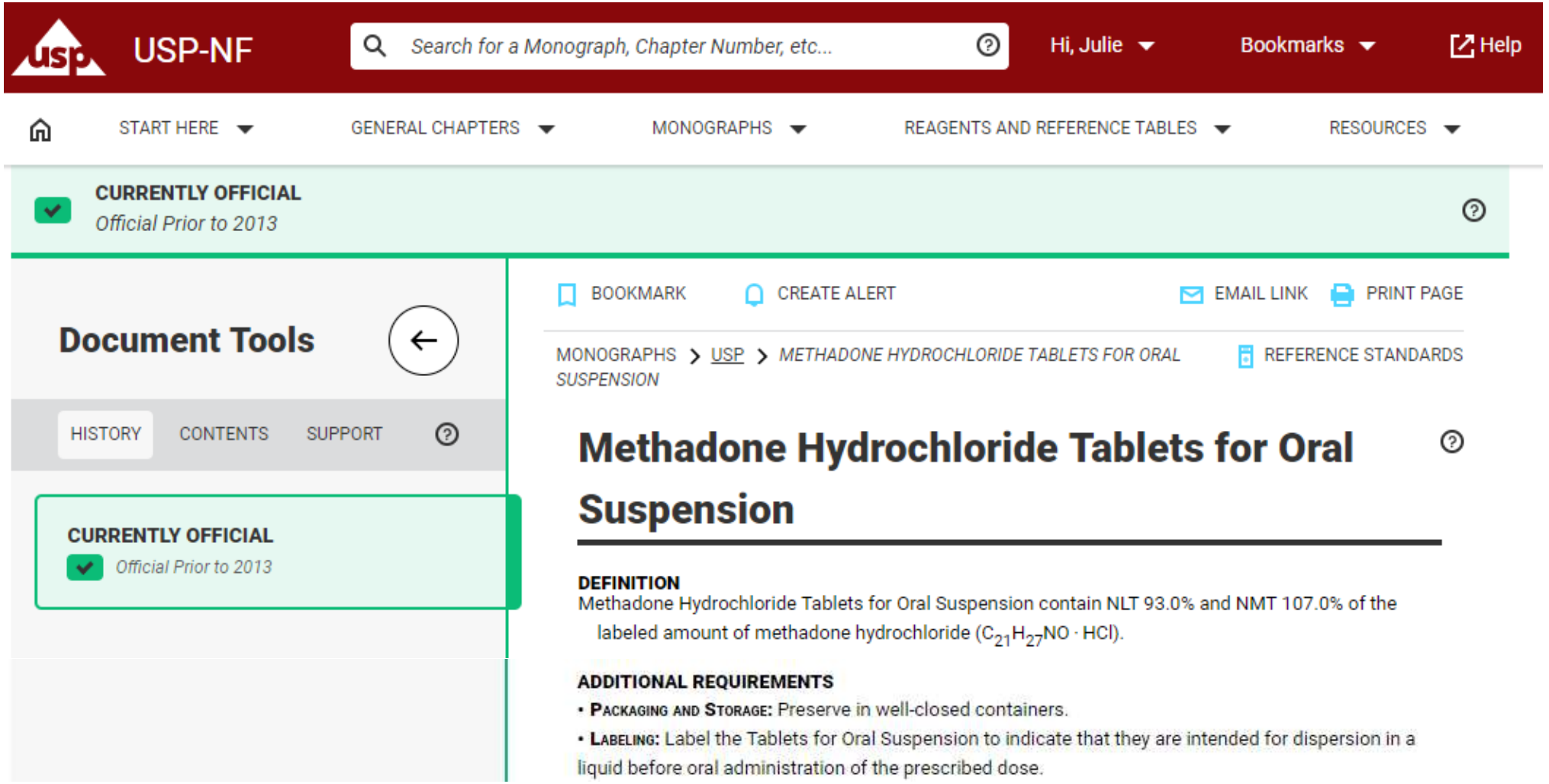
Location and Examples of Statements

- We recommend adding a statement to the end of the package insert and to the top of the Medication Guide to alert dispensers that a Medication Guide will need to be printed
    - Based on current technology, the website should display a PDF version of the Medication Guide. The link should be simple and non-promotional
    - We have provided some suggested language: “Dispense with Medication Guide available at: www.companyname/medguide/drugname.pdf”
- 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
    - For example: “Print Medication Guides at: www.companyname/medguide/drugname.pdf”

USP MONOGRAPHS

- Provide Reference Standards to:
  - Confirm accuracy and reproducibility
  - Reduce risk of ANDA rejection
  - Accelerate product development
  - Standardize any additional labeling requirements for a drug product

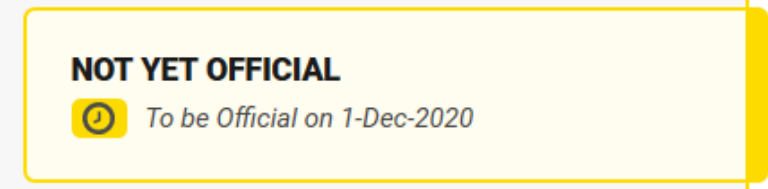
USP MONOGRAPHS (CONT.)



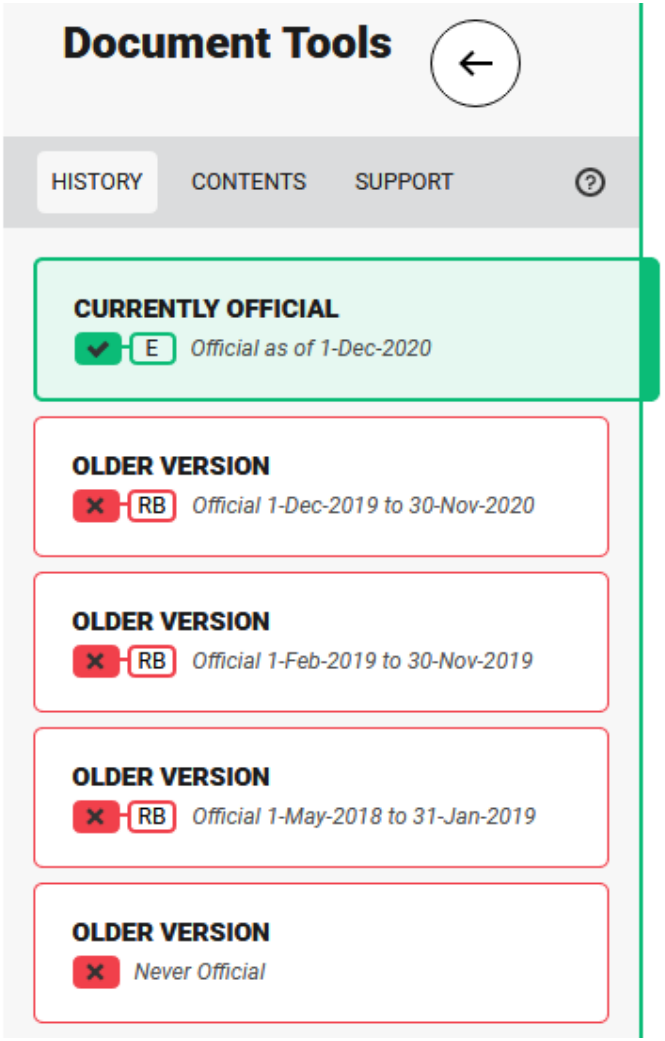
USP MONOGRAPHS (CONT.)

USP MONOGRAPHS (CONT.)

- Drug Products with an USP monograph should:
  - Use the established name that complies with the USP monograph for that drug product
  - Routinely check for USP updates @ www.uspnf.com
  - Limit the use of the “USP” descriptor to the Quality sections of the Prescribing Information (DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED)
  - Prepare for pending changes (Not Yet Official monographs). On the day that new monograph is effective your ANDA needs to meet the monograph



USP MONOGRAPHS (CONT.)

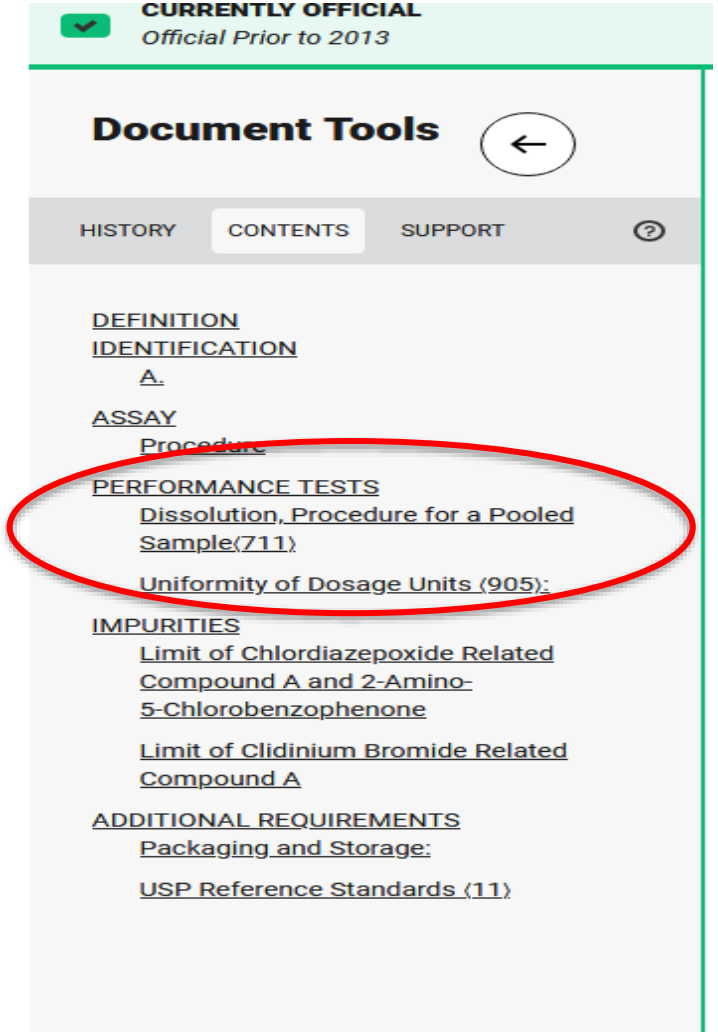


USP MONOGRAPHS (CONT.)

Dissolution Statements

- When the drug product is subject to a USP monograph, the drug product complies to the monograph standards including dissolution
- Dissolution statements should be placed at the end of the DESCRIPTION section of the Prescribing Information
- If the monograph has more than one dissolution test, indicate which test it complies to if different
- If the monograph has only one dissolution test, either comply or indicate the difference “FDA approved dissolution specifications differ from USP”
- If the USP dissolution test is pending or your drug product does not meet any of the listed USP dissolution tests, then include the statement, “FDA approved dissolution test specifications differ from USP”

USP MONOGRAPHS (CONT.)



- **Dissolution**, *Procedure for a Pooled Sample*⟨711⟩

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: Dissolve 1.92 g of sodium 1-pentanesulfonate in 900 mL of water in a 1-L volumetric flask. Adjust with dilute sulfuric acid to a pH of 3.8 ± 0.1. Dilute with water to volume.

Mobile phase: Methanol, tetrahydrofuran, and *Buffer* (6:18:75)

Standard solution: Prepare a solution having known concentrations of USP Chlordiazepoxide Hydrochloride RS and USP Clidinium Bromide RS in *Medium*.

Sample solution: Pass a portion of the solution under test through a suitable filter. Combine equal volumes of the filtered solutions and use the pooled sample for the analysis. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*, if necessary.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 212 nm

USP MONOGRAPH (CONT.)

Test 1

• **DISSOLUTION** (711)

Test 1

Buffer: 0.05 M phosphate buffer prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 900 mL of water. Adjust with 6 N sodium hydroxide to a pH of 6.8 and dilute with water to 1 L.

Medium: *Buffer*; 900 mL

Apparatus 2: 75 rpm

Time: 15 min

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 1 mg/mL of USP Atorvastatin Calcium RS in *Diluent*. Shake mechanically for 10 min or until dissolved.

Test 2 & 3

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. *Dissolution Test 2* is suitable for products labeled to contain 80 mg of atorvastatin.

Medium and **Apparatus 2:** Proceed as directed in *Test 1*.

Time: 30 min

Diluent, Standard solution, Sample solution, Instrumental conditions, and **Blank:** Proceed as directed in *Test 1*.

Tolerances: NLT 85% (*Q*) of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Buffer: Combine 250 mL of 0.2 M monobasic potassium phosphate, 112 mL of 0.2 N sodium hydroxide, and 638 mL of water. Adjust with either 0.02 N sodium hydroxide or phosphoric acid to a pH of 6.8.

Solution A: Acetonitrile, methanol, and 0.1% trifluoroacetic acid (5:5:90)

Solution B: Acetonitrile, methanol, and 0.1% trifluoroacetic acid (45:45:10)

Solution C: Dissolve 50 g of Tween 80 in 1 L of *Buffer*.

Mobile phase: See *Table 2*.

When more than one Dissolution test is given, the labeling should state the test used only if Test 1 is not used.

USP MONOGRAPHS (CONT.)

- Examples of USP statements in Labeling:
  - "Meets USP dissolution test 3"
  - "FDA approved dissolution test specifications differ from USP"
- Resolve USP statement issues as soon as possible. Last minute resolution may result in last minute changes in labeling which require re-review by DLR

USP MONOGRAPHS (CONT.)

- If a monograph becomes effective after ANDA approval:
  - Applicant is responsible for ensuring their drug product labeling complies with the requirements of the monograph
  - Labeling updates to comply with USP monograph should be submitted as an annual reportable change

PACKAGE TYPE TERMS

- The consistent use of correct package type terms is important for injectable medical products for human use in order to promote their proper use
- Refer to the guidance, *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 Guidance for Industry*

PACKAGE TYPE TERMS (CONT.)

- The package type term may differ from that of the RLD especially if the RLD was approved many years ago. If so, follow the guidance referenced on the previous slide
- Applicant should determine the proper package type term ("single-dose," "multiple-dose," or "single-patient-use" etc.)
    - The appropriate package type term appear on all components of the labeling of injectable medical products for human to include:
        - Container label and carton labeling
        - Prescribing Information
        - Labeling intended for the patient (if applicable)

PACKAGE TYPE TERMS (CONT.)

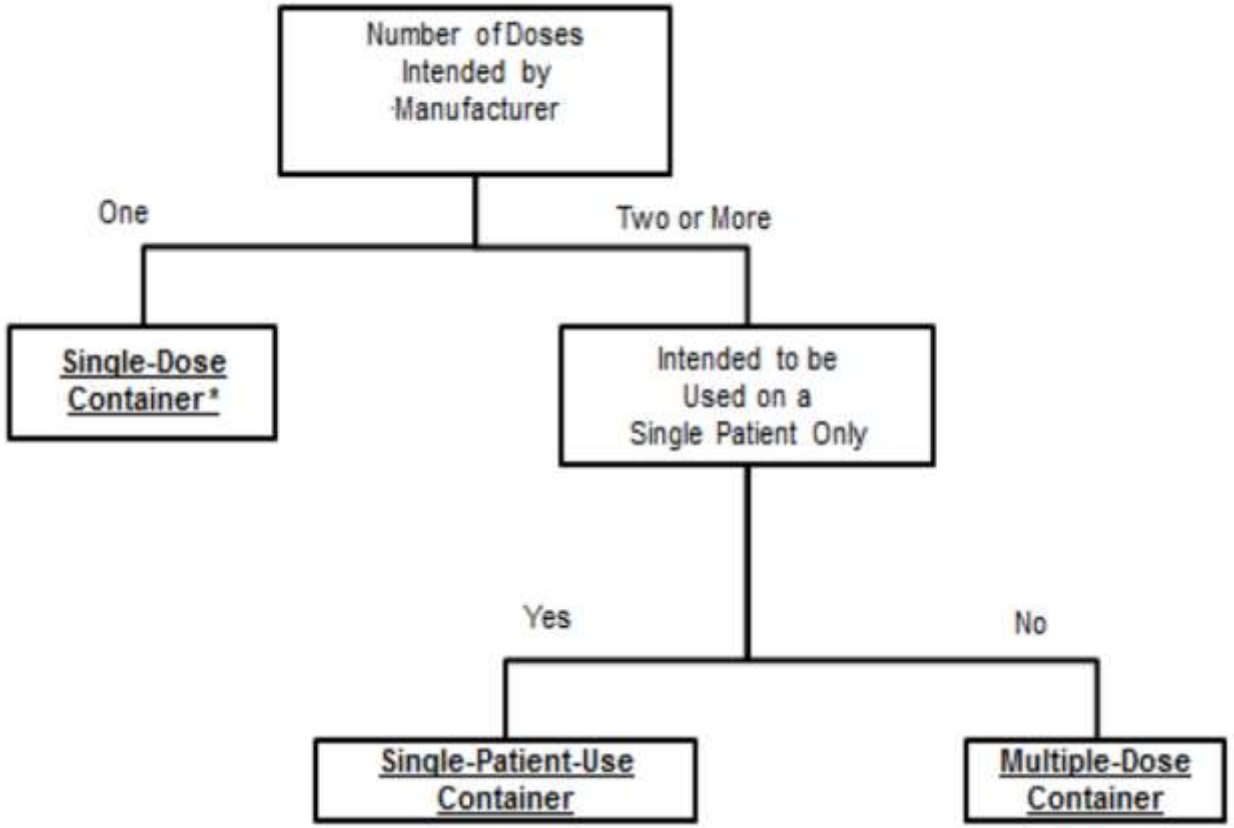
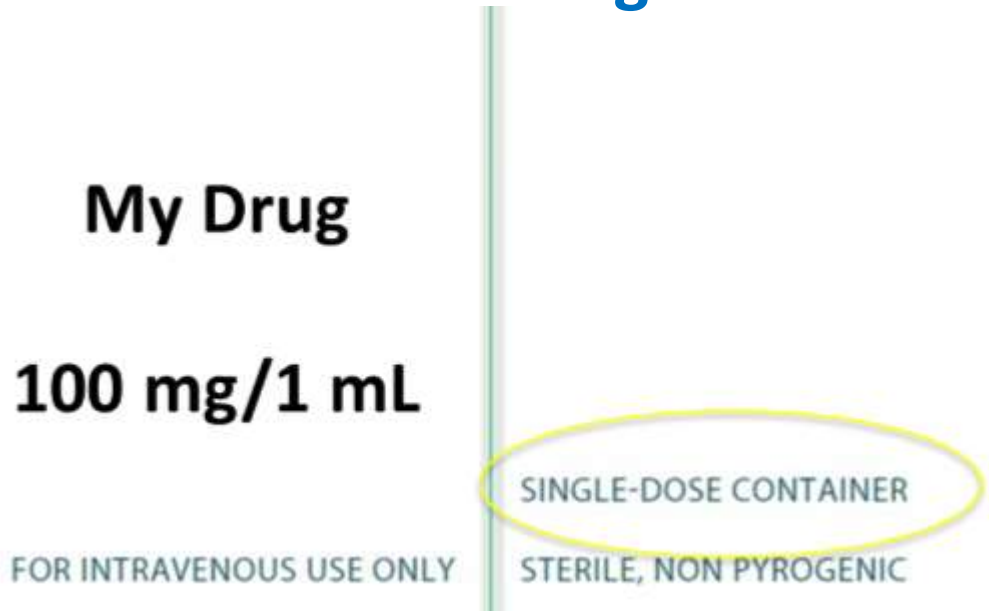


Image retrieved from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm468228.pdf

PACKAGE TYPE TERMS (CONT.)

Retired "Single-Use"

Guidance based "Single-Dose"



PATENTS/EXCLUSIVITIES & ANDAS

- Check the Orange Book (OB) for your RLD before each submission and ensure all patents and exclusivities are addressed and labeling matches the certifications and statements
- Incongruent certifications/statements and labeling will result in a deficiency and further review cycles

PATENTS/EXCLUSIVITIES & ANDAS (CONT.)

- Need to ensure that all listed method-of-use codes listed for a patent are addressed
- If information is shared amongst different codes, ensure that they are aligned with claims and submitted labeling

PATENT/EXCLUSIVITIES & ANDAS (CONT.)

Example “Meal Drug Tablets” OB Information:

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition
123456	Jun 1, 2028	U-123	Three meals a day are recommended
987654	July 4, 2029	U-776	Breakfast is the first meal of the day
987654	July 4, 2029	U-777	Breakfast is the most important meal of the day
223344	Dec 25, 2024	U-250	Lunch is the second meal of the day
232323	Jan 1, 2025	U-878	Dinner is the third meal of the day
555555	Jun 20, 2023	U-321	Snacks improve overall health
323232	Mar 10, 2027	U-456	Three meals a day are recommended; Breakfast is the most important meal of the day; Snacks improve overall health

OVER-THE-COUNTER (OTC) PRODUCTS

- Ensure labeling is up to date with the most recently approved labeling for the RLD posted at Drugs@FDA
- Ensure the Drug Facts labeling format is in accordance with 21 CFR 201.66
- Ensure the letter height or type size within the Drugs Fact labeling is in accordance with 21 CFR 201.66(d)(2) and submit a legend for all font type, size, and color

OTC PRODUCTS (CONT.)

USP Monograph Issues

- Include the USP dissolution test at the end of the “Other Information” section if Test 1 was not used. If the USP dissolution test is pending or your drug product does not meet any of the listed USP dissolution tests, then include the statement, “FDA approved dissolution test specifications differ from USP” at the end of this section

OTC PRODUCTS (CONT.)

Inactive Ingredients

- Ensure that the listed inactive ingredients match the submitted inactive ingredients in the quality modules
- Ensure that the inactive ingredients are listed in alphabetical order

OTC PRODUCTS (CONT.)

- Remember to include a toll-free number of a source to answer questions about the product. It is recommended that the days of the week and times of the day when a person is available to respond to questions also be included. Ensure the toll-free number appears no less than size 6-point font, as per 21 CFR 201.66(d)(2)
- Please ensure that the FDA toll-free number “1-800-FDA-1088” appears in the “Warnings” section of the label
- Remember to include the contact number of the poison prevention center if stating their organization on the label

TYPES OF CHANGES FOR SUPPLEMENTS

Categories for changes to an ANDA that can be submitted in a supplement, please refer to the FDA Guidance, *Changes to an Approved NDA or ANDA (Final Guidance)*

- Manufacturing Sites
- Manufacturing Process
- Specifications
- Container Closure System
- Labeling
- Miscellaneous Changes

SUPPLEMENT TYPES

Prior Approval Supplement (PAS):

Major changes requiring supplement submission and approval prior to distribution of the product made using the change

- Examples:
  - Manufacturing Sites: A move to a different manufacturing site when the new site hasn't been inspected by FDA or includes the restart of a 2-year or great discontinued site
  - Labeling: Proprietary name review and changes that are different from the RLD

SUPPLEMENT TYPES (CONT.)

Changes Being Effected (CBE):

CBE-30: Moderate changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change

- Examples:
  - Container Closure System: Changes in size/shape of container for sterile drug substance or change/addition or deleting for desiccant
  - Labeling: Reintroduction of the product into commercial market

CBE-0: Less moderate changes that allows for distribution at time of submission

- Examples:
  - Miscellaneous: Listing of new distributor information
  - Labeling: Updating labeling to provide Medication Guides in electronic format

SUPPLEMENT TYPES (CONT.)

Annual Report:

Minor changes to be described in an annual report

- Examples:
  - Specifications: Change in specification made to comply with official compendium
  - Labeling: Labeling changes made to comply with official compendium or editorial changes

SUMMARY

- Reviewed common issues regarding ANDA labeling and offered helpful tips to ensure high-quality labeling submissions which could potentially reduce review cycles

- This presentation provided general tips and recommendations into ways to improve all types of labeling submissions and avoid common errors

RESOURCES

- FDA's Prescription Drug Labeling Resources
- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (draft guidance)
- Public Availability of Labeling Changes in "Changes Being Effected" Supplements (draft guidance)
- Changes to an Approved NDA or ANDA (final guidance)
- Updating ANDA Labeling After the Marketing Application for the RLD Has Been Withdrawn (draft guidance)
- Acceptability of Draft Labeling to Support ANDA Approval (final guidance)
- Referencing Approved Drug Products in ANDA Submissions (draft guidance)
- Good ANDA Submission Practices (draft guidance)
- ANDA Submissions – Content and Format (final guidance)
- 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)
- Drugs@FDA
- Orange Book
- USP

QUESTIONS?

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