GDUFA III Labeling Updates and Tips

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Objectives

- Discuss Generic Drug User Fee Amendments (GDUFA) III updates that impact Abbreviated New Drug Application (ANDA) labeling
- Discuss best practices for ANDA labeling submissions

Background on GDUFA

- GDUFA was signed into law on July 9, 2012
- Agreement negotiated by FDA and representatives of the generic drug industry to address regulatory challenges
- Authorized every 5 years with the most recent reauthorization for fiscal years 2023 to 2027 (GDUFA III)

Division of Labeling Review (DLR)

- Ensure that the generic drug 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)(iv)
- Ensure that the labels and labeling accurately reflect the drug product information and provide sufficient information for safe and effective use of the product

Labeling Commitments in GDUFA III

- Determine whether there is a need to consult another review discipline and initiate such consults
- Strive to issue Labeling Discipline Review Letter (DRL)
  - At months 6 to 7 for ANDAs with a 10-month goal date
  - At months 5 to 6 for ANDAs with an 8-month goal date
- Limit the labeling assessment to one Information Request (IR)/DRL if other disciplines will not be acceptable during the first cycle

Labeling Commitments in GDUFA III

- Continue to assess labeling to enable an action within the assessment cycle if other disciplines are acceptable
- Minimize issuance of Complete Response Letters (CRLs) that contain only labeling deficiencies by utilizing later-cycle IRs/DRLs and the imminent action process

GDUFA III – General Best Practices

- Prominently identify (e.g., use bold font) labeling carve-outs in cover letters
  - Address all patents and/or exclusivities
  - Ensure the proposed labeling carve-out is consistent with patent certifications and exclusivity statements
- Monitor available labeling resources and make necessary revisions to labeling
  - Drugs@FDA: Updates to RLD's labeling
  - Orange Book: Updates to RLD's patents and exclusivities
  - United States Pharmacopeia-National Formulary (USP-NF): Updates to drug product monographs and USP General Chapters

Challenge Question # 1

Which resource should be used to find the RLD's last approved labeling?

a. DailyMed
b. Orange Book
c. Drugs@FDA
d. USP-NF

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Best Practices for ANDA Labeling Submissions

- Ensure Consistent Labeling Submissions
- Correct Editorial and Grammatical Statements
- Format Limitation Statement and Title
- Submit Consistent Drug Product Name and Manufacturing Statement(s)
- Adequately Differentiate Related Products and/or Product Strengths
- Recommended Format for Expiration Date
- Ensure Appropriate Labeling Statements
- Confirm Sufficient Number of Medication Guides
- Comply with Standards of Ferrule and Cap Overseal for Injectable Products
- Child-Resistant Packaging (CRP) Verification Statement
- Submit Consistent CRP Statement(s)

Ensure Consistent Labeling Submissions

- We recommend that both Microsoft Word document and PDF text versions be submitted for Prescribing Information (PI) and Patient Labeling pieces
  - Refer to the ANDA Submissions – Content and Format Guidance for Industry
- The information between the two versions should be consistent
- Ensure the documents submitted are the same as the latest RLD labeling found at Drugs@FDA

Correct Editorial and Grammatical Statements

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

- **Examples of editorial errors**
  - **Trailing zeros**: “4 mg, not 4.0 mg”
  - **Missing preceding zero**: “0.4 mg, not .4 mg”
  - **Missing comma**: “1,000 not 1000”
  - **Spacing error**: “Place one drop twicedaily” vs. “Place one drop twice daily”
  - **Duplicate text**: “Place one drop twice drop twice daily” vs. “Place one drop twice daily”
  - **Spelling**: "Place on droop twiece dailyy"

Format Limitation Statement and Title

- HIGHLIGHTS OF PRESCRIBING INFORMATION: The Limitation statement and Title (as shown below) should be in accordance with the Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements Guidance for Industry:

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

  [NAME OF DRUG PRODUCT] [dosage form] [route of administration]

Submit Consistent Drug Product Name and Manufacturing Statement(s)

- Drug Product Name
  - Ensure references to the drug substance and drug product are consistent throughout the PI. Use the established name (i.e., dosage form included) when referring to the drug product

- Manufacturing Statement(s)
  - Place of business of manufacturer, packer, or distributor: include one of the qualifying statements found in 21 CFR 201.1(h)(5) or (6) on the drug product labels and labeling
  - Make sure this information is consistent across all labeling pieces where it is listed/required

Adequately Differentiate Related Products and/or Product Strengths

- Use a method to better distinguish the different strengths of the drug product
- Use a method to further differentiate the proposed product labels from your other related products
- E.g., boxing, contrasting colors, and/or some other means
- Refer to the Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance for Industry

Recommended Format for Expiration Date

- Recommended formats for expiration date include a 4-digit year
- Use a hyphen or forward slash to separate the portions of the expiration date
- Recommended abbreviations for expiration date
  - EXP.; EXP; EXPIRY, EXP DATE; Exp. Date

- Example: If using only numerical characters are used
  - YYYY-MM-DD
    - 2023-04-30 OR 2023/04/30
  - YYYY-MM (if space is limited)
    - 2023-04 OR 2023/04
- Example: If using alphabetical characters to represent the month
  - YYYY-MMM-DD
    - 2023-APR-30 OR 2023/APR/30
  - YYYY-MMM (if space is limited)
    - 2023-APR OR 2023/APR

Ensure Appropriate Labeling Statements

- **Injectable 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 the 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.

- **Injectable 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 the Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance for Industry.

- **Gluten:**
  - “Gluten Free” is not acceptable. We recommend “Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).” Refer to the Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry.

- **Warning Statement for Rubber:**
  - “Latex-Free” is not acceptable. 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(d).

- **Inactive Ingredients:**
  - Special labeling statements and regulatory requirements (note: this is not an exhaustive list):
  - FD&C Yellow No. 5 (tartrazine)
  - Aspartame
  - Sulfite
  - Refer to 21 CFR 201.20 (b), 21 CFR 201.21(c), 21 CFR 201.22(c), and 21 CFR 201.22(b).

Confirm Sufficient Number of Medication Guides

- Provide a statement that a sufficient number of Medication Guides are available for dispensing and distribution for your drug product in Module 1.14.1 and/or Question-based Review (QbR)
- Refer to 21 CFR 208.24(b)

Comply with Standards of Ferrule and Cap Overseal for Injectable Products

- Comment in Module 3.2.P.7 as to whether text appears on your cap/ferrule overseal, and also comment on the color of your cap

- Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals
  - A cautionary statement is intended to prevent an imminent life-threatening situation and may include instructional statements that provide potency or other safety-related instructions if warranted
  - If no cautionary statement is necessary, the ferrule and cap overseal must remain blank

Comply with Standards of Ferrule and Cap Overseal for Injectable Products

- Only cautionary statements may appear on the top (circle) surface of the ferrule and cap overseal
- If a cautionary statement is necessary, provide a high-resolution image of your ferrule and cap overseal in Module 3.2.P.7 and ensure there is adequate contrast between the proposed text and color of the ferrule and cap overseal

Child-Resistant Packaging (CRP) Verification Statement

- Ensure your proposed packaging meets the requirements of the Poison Prevention Packaging Act (PPPA)
- A written verification that your product's packaging meets the U.S. Consumer Product Safety Commission's (CPSC's) child-resistant packaging standards in Module 3.2.P.7 is encouraged
- An example of a written verification may be "We verify in this submission that the following package (or packages) meet U.S. Consumer Product Safety Commission's (CPSC's) standards under 16 CFR 1700."

Submit Consistent CRP Statement(s)

- If including CRP information in the PI and Patient Labeling, it should appear in the:
  - “HOW SUPPLIED/STORAGE AND HANDLING” section of the PI and
  - “How should I store Drug X?” section of Patient Labeling
- The CRP statement(s) in the PI and Patient Labeling should be consistent.
- Location of CRP Statement(s)
  - For prescription drug container label/carton labeling, display the CRP statement on the side panel in close proximity to storage information
  - For non-prescription (OTC) drug labeling, display the CRP statement in the Drug Facts labeling under the subheading "Other information"
- Refer to the Child-Resistant Packaging Statements in Drug Product Labeling Guidance for Industry

Challenge Question # 2

Which of the following statements is **TRUE?**

a. Cautionary statements may appear on the side surface of the ferrule and cap overseal
b. Consistent Microsoft Word document and PDF text versions should be submitted for PI and Patient Labeling pieces
c. “Gluten Free” is an acceptable labeling statement
d. Different strengths of the proposed drug product should not be adequately differentiated, e.g., boxing, contrasting colors, and/or some other means

Challenge Question # 2

Which of the following statements is **TRUE?**

a. Cautionary statements may appear on the side surface of the ferrule and cap overseal

b. Consistent Microsoft Word document and PDF text versions should be submitted for PI and Patient Labeling pieces

c. “Gluten Free” is an acceptable labeling statement

d. Different strengths of the proposed drug product should not be adequately differentiated, e.g., boxing, contrasting colors, and/or some other means

Best Practices for ANDA Supplements

- Detailed Cover Letter
- Ensure Complete Submission
- Patents and Exclusivities
- Side-by-Side Comparisons
- Electronic Patient Labeling (URLs)
- Food and Drug Administration Amendments Act (FDAAA) Safety Labeling Changes (SLCs)

Detailed Cover Letter

- Clearly and accurately state the proposed changes in the cover letter
- For CBE-0 RLD updates, state the NDA number, supplement number, and the date of approval of the reference supplement
  - e.g., “…labeling updates in accordance with the reference listed drug (RLD), DRUGNAME, NDA XXXXX/S-XXX approved on XX/XX/XXXX.”

Ensure Complete Submission

- Note that DLR does not issue acknowledgement letters for CBE-0s
- If DLR requests for an *amendment* to a *specific* supplement, do not submit a new supplement. Submit an amendment to the referenced supplement
- For ANDAs with shared Prescribing Information, provide submissions for *each* ANDA
  - e.g., ANDA A and B share an insert, if a CBE-0 is submitted to ANDA A for labeling updates to be in accordance with the RLD, applicant should submit a CBE-0 for ANDA B as well

Patents and Exclusivities

- Ensure that the proposed labeling is consistent with patent certifications and exclusivity statements
- For labeling carve-outs to align with an Agency-issued BPCA template, also address the new exclusivities listed in the Orange Book
- New labeling carve-outs due to exclusivities should be submitted as a PAS not as a CBE. Submissions to align with an Agency-issued BPCA template should be submitted as a CBE

Side-by-Side Comparisons

- Provide a side-by-side comparison of:
  - Approved RLD labeling vs. Proposed ANDA labeling

    OR
  - Previously approved ANDA labeling vs. Currently proposed ANDA labeling
- For amendments, note and submit what was requested in the issued letter
- When submitting a Prior Approval Supplement (PAS), also provide a side-by-side comparison with the previously approved labeling, the RLD (if applicable), and the proposed labeling

Electronic Patient Labeling (URLs)

- Do **not** *replace* the standard Medication Guide statement (per 21 CFR 208.24(d)) with a URL on container and carton labeling. A URL may be placed, in addition, to the standard statement provided that it meets the requirements of 21 CFR 610.60
  - e.g., “Dispense the Medication Guide available at [include URL], to each patient.”
- Add a statement to the top of the Medication Guide to alert dispensers that a Medication Guide will need to be printed and dispensed
  - e.g., “Dispense with Medication Guide available at www.companyname/medguide/drugname.com.”
- The Medication Guide dispensing statement should be included on all labeling (container/carton, PI, and Medication Guide)

Electronic Patient Labeling (URLs)

- Note the URL link should be simple, non-promotional, and not false or misleading
- Ensure consistency of the URL link in all proposed labeling pieces
- Patient Information Leaflets can also be supplied electronically and submitted as a CBE-0

FDAAA Safety Labeling Changes (SLCs)

- Proposed labeling should include language *identical* to what is delineated in the SLC notification letter
- Submit a side-by-side comparison of the previously approved labeling with the new SLC language

Summary

Adherence to ANDA labeling best practices facilitates the labeling review process and enables the fulfillment of GDUFA III labeling commitments – resulting in the approval of safe and effective generic drugs for the American public

Resources

- FDA's Labeling Resources for Human Prescription Drugs
- Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (Final Guidance)
- GDUFA III Commitment Letter
- Good ANDA Submission Practices (Final Guidance)
- ANDA Submissions – Content and Format (Final Guidance)
- Referencing Approved Drug Products in ANDA Submissions (Final Guidance)
- Acceptability of Draft Labeling to Support ANDA Approval (Final Guidance)
- Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn (Draft Guidance)
- Changes to an Approved NDA or ANDA (Final Guidance)
- Public Availability of Labeling Changes in "Changes Being Effected" Supplements (Draft Guidance)
- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Final Guidance)
- Safety Considerations for Product Design to Minimize Medication Errors (Final Guidance)
- Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers (Final Guidance)
- Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (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)
- Child-Resistant Packaging Statements in Drug Product Labeling (Final Guidance)
- Gluten in Drug Products and Associated Labeling Recommendations (Draft Guidance)
- Drugs@FDA
- Orange Book
- United States Pharmacopeia (USP) and the National Formulary (NF)

Thank you for your attention!

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