

Generic Drug Labeling: Strategies for Providing High-Quality Submissions

CAPT Lillie Golson, Deputy Director

Division of Labeling Review

Food and Drug Administration/Office of Generic Drugs

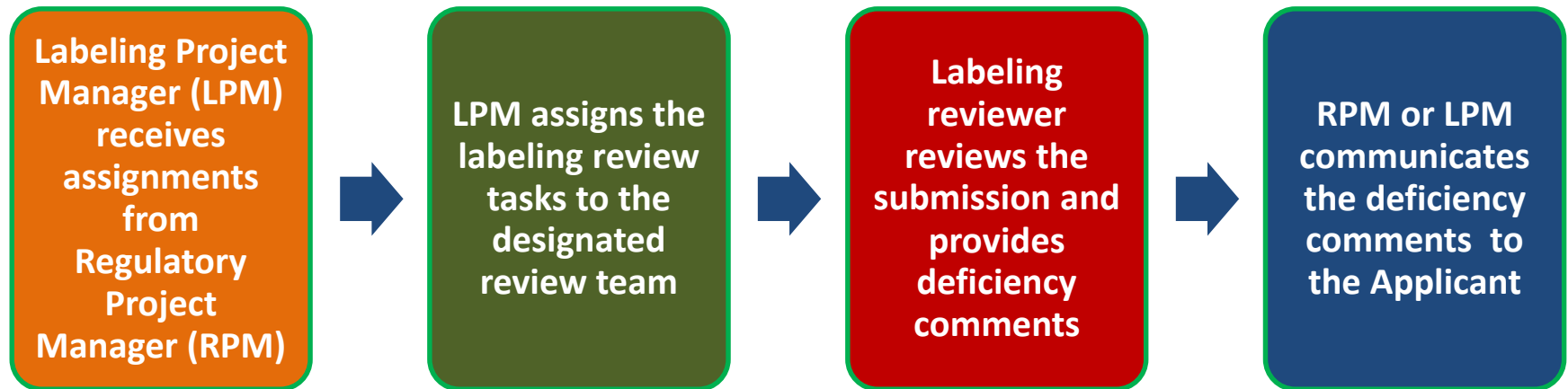
REdI: Generic Drug Forum

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Outline

- Provide a brief overview of the labeling review process
- Provide responses to the questions most frequently asked by Industry
- Recommend useful strategies to reduce review cycles and provide high-quality labeling submissions

Labeling Review Process



Communicating Deficiencies

- ECD – Easily Correctible Deficiency
 - Labeling-only comments sent via email by the LPM to the contact listed on the 356h Form.
 - Applicant has 10 business days to respond in most cases.
- CR – Complete Response
 - Sent by the RPM with deficiencies from other disciplines.
 - Sent by the LPM for labeling only deficiencies.
- Applicant responds, and the process is repeated again, often for multiple cycles.

**So, why the back and forth
multiple times?**



Unanswered
questions

Directions
unclear

Confusion

Conflicting
information

Unasked
questions

New
Unexplained
Changes



Which product labeling should be used as model labeling when NDA/RLD is discontinued?

- The NDA RLD should be used for labeling comparisons, even if discontinued.
- The content of labeling should be the same as the NDA RLD, **including the product's nonproprietary name.**
- Efforts are actively being made to have the NDAs, both active and discontinued, update their labeling.

Doing so...

- Enables ALL ANDAs to update labeling promptly.
- Allows for more extensive revisions, if warranted.



Does this also apply to FDAAA Safety Labeling Changes for discontinued products?

- Under section 505(0)(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products *and* to products that are *not marketed* (e.g., discontinued), unless approval of the product has been withdrawn and posted in a Federal Register notice.
- Remember, if you submit language different from what is in the Notification Letter, you must submit as a Prior Approval Supplement within 30 days of the Notification Letter.
- If you agree with the proposed language, you may submit as a CBE-0.

Which product labeling should be used as model labeling when the NDA RLD is withdrawn?

A Guidance for Industry titled:

Referencing Approved Drug Products in ANDA Submissions issued January 2017:

- Defines Reference Listed Drug (RLD), Reference Standard (RS), and Basis of Submission.
- Re-emphasizes that labeling can only model after the NDA RLD.
- Provides an alternate means, other than FOIA, for obtaining labeling to compare your submission to. See highlighted section of Footnote 28 of the guidance below.

²⁸ An applicant is responsible for checking appropriate sources in order to obtain the RLD labeling. In instances where the RLD labeling cannot be located, an applicant for convenience initially may compare its proposed generic drug's labeling with the labeling of another ANDA that referenced the same RLD and currently is marketed. Prior to approval, the applicant may need to revise labeling to reflect certain updated information that would have been necessary had the RLD not been withdrawn. See FDA's draft guidance for industry on *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016).

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536962.pdf>

What labeling should I use for my side-by-side comparison?

- When there is an RLD, submit a side-by-side with the new 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.
- Make certain your side-by-side comparison is well annotated, especially for more complex drug products.

What labeling pieces can be submitted in draft?

- **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>



What is the most efficient way to submit the same labeling change to both an NDA and an ANDA when the applicant owns both the NDA and the ANDA?

- 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.

Who is responsible for distributor labeling?

- As the ANDA holder, you 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 often times 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 is updated on The DailyMed website.
- Note that your distributor labeling should not be submitted with CBE-0 supplements, unless it is the subject of the submission.

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

Who do I contact if I have questions?

To ensure more timely responses, please direct inquiries to the contacts designated below:

- For a specific ANDA – Contact the RPM or LPM assigned to the ANDA.
- For other questions – Email GenericDrugs@fda.hhs.gov.

Recommended Strategies

Valuable strategies for providing high-quality labeling submissions

- 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).
- 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.



Valuable strategies for providing high-quality labeling submissions (cont.)

- Before submitting labeling amendments, check Drugs@FDA, the Orange Book, and USP for updates. Not submitting the most up-to-date labeling results in an automatic deficiency! This could be particularly problematic when a goal date is near.
- Refrain from making *unnecessary* unsolicited changes to your labeling, especially right before approval. Inadvertent mistakes are often made requiring correction before the application can be approved.
- At the time of approval, labeling must be the same as the last approved labeling of the reference listed drug, except for allowable differences.

Valuable strategies for providing high-quality labeling submissions (cont.)

- For drug products manufactured in a foreign country, include the country of origin on the label/labeling (See 21 CFR 201.1(i)).
- When submitting supplements for manufacturing site changes, please do not submit a labeling supplement 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 submitted in an Annual Report.



Valuable strategies for providing high-quality labeling submissions (cont.)

- Ensure that your 356(h) Form is up-to-date.
- Report any U.S. Agent POC changes as soon as possible, especially email address changes.
- If possible, list additional person(s) on the 356h Form to serve as alternate POCs, in case the primary POC is not available.
- Make certain your authorized representatives on the 356h Form have secure email addresses.

*Thank
You*

Please complete the session survey:
surveymonkey.com/r/GDF-D2S06