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Labeling Development and Lifecycle Maintenance – Industry Strategies and Best Practices

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Disclaimer

• This presentation reflects the speaker's perspective on this topic and does not necessarily represent the views of Mylan.

Objectives/Overview

- ANDA Labeling Requirements
- **Development of Labeling in Support of Original ANDA Filing**
- **Labeling Responsibilities for a Pending Application**
- **Labeling Responsibilities for an Approved Application**
- **General Tips and Helpful Hints**
- **References and Resources**

ANDA Labeling Requirements

- An Abbreviated New Drug Application (ANDA) generally must contain information to show that the proposed generic product is:
    - the same as the Reference Listed Drug (RLD) with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences*)
    - bioequivalent to the RLD

ANDA Labeling Requirements

- *“Certain permissible differences” include differences approved under a petition (filed under 314.93) or because the proposed generic drug product and RLD drug product are produced or distributed by different manufacturers (including differences in expiration date, formulation, bioavailability, or pharmacokinetics); labeling revisions made to comply with current FDA labeling guidances; or omission of indication/aspect of labeling protected by patents and/or exclusivities.

ANDA Labeling Requirements

- For FDA to issue approval upon action date, the ANDA labeling must reflect the latest approved labeling revisions for the RLD, except for permitted differences*
- *ANDA can be finally approved with labeling that differs from RLD due to a labeling revision if:
    - RLD labeling revision is approved within 60 days of expiration of patent, exclusivity or 30-month stay delaying ANDA approval
    - RLD labeling revision does not impact “Warnings and Precautions” section of the prescribing information

ANDA Labeling Requirements

- FDA determines that presence of previous version of the labeling will not adversely impact safe use of drug product; and
- ANDA sponsor commits to submit CBE with revised labeling within 60 days after notification date

Development of Labeling in Support of Original ANDA Filing

- Start as early as possible since there are so many components
- Ensure that you use most recently approved RLD labeling as your basis (Drugs@FDA website)
- Ensure drafted labeling aligns with your product's formulation and packaging presentation(s)
    - Use CMC Module 3 documents as validation source
    - DOSAGE FORMS AND STRENGTHS section
    - DESCRIPTION section
    - HOW SUPPLIED section
- Engage Legal department to assess patent certification and exclusivity strategy – carve outs may be necessary

Development of Labeling in Support of Original ANDA Filing

- Assess for USP drug product monographs and compliance strategy
- Engage with packaging site(s) for key lines for packaging components to ensure that textual alignment, bar code placement, and lot number, expiration date, serialization information placement is accurate
- Engage with Marketing department to ensure that branding elements and overall packaging design are acceptable
- The container labels submitted “should reflect the content as well as an accurate representation of the layout, text size and style, color, and other formatting factors that will be used with the final printed labeling”

Labeling Responsibilities for a Pending Application

- First cycle review approval is the goal!
- Day 1 launches are key! Final printed artwork can be a rate-limiting factor in launch readiness when last minute revisions are required:
    - Location of packaging site - if outside U.S., additional challenges
    - Characteristics of drug product – supply chain storage requirements and sterility must be taken into consideration
    - Time associated with obtaining revised artwork components
    - Cost – to applicant/distributor and to healthcare industry

Labeling Responsibilities for a Pending Application

- Under Generic Drugs User Fee Act (GDUFA) reauthorization for fiscal years 2018 to 2022 ("GDUFA II") – Initial labeling reviews are conducted early in the review process
- Discipline Review Letters (DRL) are issued at about mid-point of review (sometimes as early as 3-4 months after filing date)
- Feedback is given when labeling is found to be acceptable and no deficiencies are found upon initial review

Labeling Responsibilities for a Pending Application

- Continuously monitor for approved RLD labeling supplements and efficacy supplements
- Subscribe to get daily email notices of approvals from the Agency (www.fda.gov/drugs/news-events-human-drugs)
- Continuously monitor the Approved Drug Products with Therapeutic Equivalence Evaluations (“Orange Book”) for newly listed patents, use codes and marketing exclusivities
- Monitor USP website for new drug product monographs or revisions to existing monographs (www.uspnf.com)

Labeling Responsibilities for a Pending Application

- Under GDUFA II, late stage RLD labeling updates still have the ability to delay approval of ANDAs
    - Unsolicited Labeling Amendments = 3 months added to goal date
- Under GDUFA II, late stage addition(s) of patents/exclusivities to the Orange Book (with labeling implications) still have the ability to delay approval of ANDA application(s)
    - Potential delay in close of labeling review due to complexities of review of sponsor's proposed carveouts or development of standardized labeling template

Labeling Responsibilities for an Approved Application

- Submit Structured Product Labeling (SPL) for drug listing within 14 days of approval of application. SPL should reflect the version of labeling approved with the application
- For the marketing life of the product, update drug listing with each labeling revision
- If labeling has not been revised in a calendar year, certify the existing listing with a “blanket no change certification”
- Make sure to appropriately delist discontinued package sizes and product strengths as last lots manufactured expire

Labeling Responsibilities for an Approved Application

- Monitor for approved RLD labeling updates
- Gratuitously submit Special Supplements – Changes Being Effected to comply with the RLD updates
- In some instances, the Agency will email ANDA sponsors to request compliance with the most recently approved RLD labeling (typically with a 30 day response request)
- If the application was approved with carveouts in the labeling, be ready to submit revised labeling to include the previously carved out information upon expiry of associated patent or exclusivity

Labeling Responsibilities for an Approved Application

- Be aware that RLD sponsors may obtain additional exclusivities post approval of generic competition, so continue to monitor the Orange Book for new exclusivities associated with RLD labeling updates
- Be proactive in reviewing new labeling guidances and regulations issued by the Agency that impact generic labeling
- The guidances occasionally provide for actions that can be taken by generic applicants without waiting for the RLD labeling to update first
    - Susceptibility Test Interpretive Criteria Labeling Guidance
    - Pregnancy and Lactation Labeling Rule (PLLR)
    - Package Type Terms and Recommendations for Injectable Products

Labeling Responsibilities for an Approved Application

- Safety Labeling Changes Under Section 505(o)(4) of the FD&C Act
- Applies to ANDAs “without a currently marketed RLD approved under an NDA”
- Regardless of whether or not the ANDA product is being actively marketed, sponsor must respond to request in 30 calendar days by either adopting the Agency’s labeling revisions verbatim, proposing different text for the Agency’s review, or submitting a rebuttal statement with rationale explaining why the requested change is not warranted
- Once safety labeling changes are approved for the (marketed) RLD, prioritize adopting the revisions for your impacted ANDA(s)

General Tips and Helpful Hints

- Submit draft labeling for prescribing information revisions during the the review of pending applications
    - prescribing information is the most likely component to change due to RLD labeling revisions
    - draft labeling can typically be prepared more quickly, thereby minimizing goal date extension when less than three months away from goal date
    - “catch up” with artwork to support launch
- Good communication between Regulatory Affairs teams if discipline responsibility is divided as there are often Quality deficiencies that can impact labeling

General Tips and Helpful Hints

- Be proactive in communication with the Agency at any stage in product lifecycle if questions arise
- Be proactive in communication with other internal departments and/or third party partners when labeling revisions are needed
- For companies with large portfolios, completing a Labeling History is helpful (even though it is not required for submission by the Agency)
- Keep informed of new guidances and regulations issued by the Agency and take advantage of opportunity to submit comments to the docket
- When possible, combine multiple updates into one labeling revision to minimize submission to the Agency and versions of artwork

General Tips and Helpful Hints

- When developing a new marketing/branding presentation for an existing portfolio or developing one for a new company/subsidiary, vet the desired presentation with the Division of Labeling Review
- When preparing annotated comparisons in support of submissions, compare back to the approved RLD labeling when there has been an RLD labeling revision since your previous submission
- You can never review labeling documents enough in support of submissions – always use new versions of labeling as an opportunity to double check product-specific characteristics and application history

References and Resources

- 505(j)(2)(A)(v) of FD&C Act
- 21 CFR 314.94(a)(8)(iv)
- 505(j)(10) of FD&C Act
- GDUFA II Commitment Letter
- Guidance for Industry – Acceptability of Draft Labeling to Support ANDA Approval (October 2015)
- 81 FR 60169
- 21 CFR 207.57
- Guidance for Industry – Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs (December 2017)

References and Resources

- 79 FR 72064
- Guidance for Industry - Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2014)
- 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 (October 2018)
- 505(o)(4) of the FD&C Act