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Review Article

Regulatory framework for USFDA regulated drug product labeling update

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ABSTRACT

The regulatory framework for USFDA-regulated drug product labeling updates is crucial for ensuring the accuracy and comprehensiveness of prescribing information. This article provides an overview of the two formats used in prescribing information: the old format and the Physician Labeling Rule (PLR) format. It explains the sections included in the PLR format, such as indications and usage, dosage and administration, contraindications, warnings and precautions, adverse reactions, drug interactions, and more. This article gives an overview of OTC labeling, key elements that are mandated, safety-driven label change, and regulatory process by the FDA. The article also discusses the implementation of safety-related labeling changes (SrLC) describing the process of notifying and responding to the applicant(s) and addressing the evaluation procedures. The revision of Abbreviated New Drug Application (ANDA) labeling based on the Reference Listed Drug (RLD) labeling will be discussed and information will be provided about the supporting documents for the change. Overall, this article provides valuable insights into the regulatory framework for updating drug product labeling in the United States, ensuring that healthcare professionals have accurate and up-to-date information for safe and effective medication use.

Keywords:
Label update, ANDA label, SrLC, PLR Format, OTC Label, RLD label, Non-PLR format, PIL

1. INTRODUCTION

Prescribing information is a document that contains detailed information about a medication, including its approved indications, dosages, administration, contraindications, warnings, precautions, adverse reactions, and other important information. The U.S. Food and Drug Administration (FDA) approves this document, which is intended to be a comprehensive and reliable source of information for healthcare professionals (e.g., doctors, nurse practitioners, physician assistants, pharmacists, nurses), patients, and caregivers (medication guides empower to make informed decisions, recognize potential adverse effects, and take appropriate actions)[1].

Labeling: all labels and other written, printed, or graphic matters upon any article (or its containers or wrappers) or accompanying the article. Examples of Labeling for prescription drugs include:

- FDA-approved patient labeling
- Carton/container labeling
- Prescribing information

Labels: a display of written, printed, or graphic matter upon the immediate container of any article. For example: Container label[2].

The FDA issued a final regulation on January 24, 2006, which modified the guidelines regarding the content and presentation of labels for prescription drugs and biological products intended for human use[3].

1.1. Prescribing information formats[4].

Two formats have been used in Prescribing Information: the old format and the PLR (Physician Labeling Rule) format. These old formats are no longer commonly used but may still be encountered in certain contexts.

1.1.1. Non-PLR or old format

The old format refers to the previous format of Prescribing Information used in the United States before

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the implementation of the current FDA (PLR) format. This format had a different organization and section headings compared to the current format. The old format was revised to improve clarity and readability, leading to the adoption of the current FDA format.

The details provided in non-PLR format are. Description, Clinical Pharmacology, Contraindications, Indications and Use, Warnings, Precautions, Adverse Reactions, Drug dependency and abuse, administration, dosage, and overdosing, How Supplied, and Other Sections: Clinical Study, Animal Toxicity, and (or) Animal Pharmacological studies.

1.1.2. PLR format

The PLR format was a format used by the FDA for the labeling of prescription drugs. It aimed to enhance the clarity and usefulness of the information provided to healthcare professionals. The PLR format focused on presenting key prescribing information in a standardized and concise manner. The PLR format was designed to be more user-friendly and easier to navigate compared to the old format.

The typical format of Prescribing Information (PLR Format) includes the following sections[5-6]:

- Indications and usage: This section outlines the approved uses of the medication and provides a brief description of the conditions it is intended to treat.
- Dosage and administration: This section provides detailed information on the recommended dosage, frequency, and route of administration for different patient populations (e.g., adults, children, elderly). It may also include instructions on dose adjustments in special populations or in the presence of specific medical conditions.
- Dosage forms and strength: This section lists the various forms in which the medication is available and provides the available strengths or concentrations of the medication. It typically includes the amount of active ingredient per unit of the dosage form (e.g., milligrams for tablets or capsules, milligrams/milliliters for solutions) or a description of the concentration (e.g., the percentage in creams or ointments).
- Contraindications: This section lists situations or conditions in which the medication should not be used due to the potential for harm or lack of efficacy. It may include specific patient populations, concurrent medications, or medical conditions to be avoided.
- Warnings and precautions: This section highlights important safety information, potential risks, and precautions associated with the medication. It may include specific warnings related to organ toxicity, allergic reactions, or other serious adverse events.
- Adverse reactions: This section provides a comprehensive list of the most commonly reported adverse reactions associated with the medication. It could provide details on the appearance, the degree of severity, and potential treatment of these reactions.
- Drug interactions: This section describes potential interactions between the medication and other drugs, food, or substances. It may include information on the effects of concomitant use and recommendations for dose adjustments or monitoring.
- Use in special populations: This section describes how to use the drug in particular patient groups, including children, pregnant or nursing women, and patients suffering from hepatic or renal disorders.
- Drug abuse and dependence: If applicable, this section describes the potential for drug abuse, dependence, or withdrawal symptoms associated with the medication.
- Overdosage: This section provides information on the symptoms, management, and treatment of an overdose with medication.
- Description: This part includes an outline of the drug's pharmacology, the mechanism of action, and physical characteristics.
- Clinical pharmacology: This section provides detailed information on medicine's pharmacodynamics (how the drug impacts the body) and pharmacokinetics (absorption, distribution, metabolism, and excretion).
- Non-clinical toxicology: This section includes information from non-clinical (animal) studies regarding the drug's potential toxicity, reproductive effects, or carcinogenicity.
- Clinical studies: This section summarizes the clinical studies conducted to prove the drug's safety and efficacy. It may include information on study design, patient populations, and primary endpoints.
- References: This section lists the references cited throughout Prescribing Information.
- How supplied, storage, and handling: It provides information on packaging, storage conditions, and the shelf life of the medication.
- Patient counseling information: It includes important information that healthcare professionals should discuss with patients, such as potential risks, benefits, and instructions for use.

According to FDA, the "Medication Guide" is an educational document that provides important information about the safe and effective use of certain prescription medications. Medication guides are intended to inform patients and caregivers about specific risks, benefits, and instructions associated with the medication[7].

Medication guides are written in patient-friendly language to ensure that the information is easily understandable by individuals without a medical background. The content is designed to empower patients to make informed decisions about their treatment and to enhance their understanding of the medication they are taking.

Medication guides follow a standardized format, which includes specific sections and headings to provide clear and organized information. This format helps patients locate and understand the relevant information they need.

1.2. OTC labeling and its elements

According to the U.S. Food and Drug Administration (FDA), "OTC labeling" refers to the information and instructions provided on the label or packaging of over-the-counter (OTC) drug products. The FDA has established specific regulations and requirements for OTC labeling to ensure that consumers have access to accurate, clear, and helpful information about these products[8].

OTC labeling includes various elements that are mandated by the FDA, including:

- Drug Facts panel: The Drug Facts panel is a standardized section of the OTC label that provides key information about the product's active ingredients, uses, warnings, directions for use, and other important details. It follows a specific format and layout to ensure consistency and ease of understanding.
- Active ingredients: OTC labels must list the active ingredients, which are the substances responsible for the intended effects of the product. Active ingredients are typically listed with their generic names and their respective strengths.
- Uses: This section of the label describes the conditions or symptoms for which the OTC drug product is intended to be used. It provides a concise description of the specific purposes or indications for using the product.
- Warnings and directions: OTC labeling includes prominent warnings and precautions to inform consumers about potential risks, side effects, contraindications, and other important safety information. It also provides clear and specific directions for proper use, including dosage instructions, administration methods, and any other relevant instructions for different age groups or populations.
- Other Information: OTC labels may include additional information such as storage instructions, expiration dates, inactive ingredients, tamper-evident packaging statements, contact information for the manufacturer or distributor, and other relevant details.

The FDA regulates OTC labeling to ensure that it is accurate, informative, and understandable to consumers. OTC drug manufacturers, packers, and distributors are required to comply with these labeling requirements to provide consumers with the necessary information to make informed decisions about the safe and effective use of OTC drug products.

Safety-driven label changes can occur for various reasons, including new safety concerns, emerging scientific data, adverse event reports, or changes in the regulatory landscape.

Here are some common safety-driven label changes that the USFDA may require for OTC drugs:

- New safety information: If new safety concerns or risks associated with an OTC drug are identified, the FDA may require manufacturers to update the labeling to reflect these risks. This could include adding warnings, precautions, or contraindications.
- Dosage and administration instructions: The FDA may revise the dosage and administration instructions to ensure that consumers use the OTC product safely and effectively. This may include clarifying dosing instructions for different age groups or populations.
- Labeling for specific populations: Labeling changes may be made to provide specific instructions for vulnerable populations, such as pregnant or breast-feeding women, children, or the elderly.
- Drug interactions: If new information becomes available about potential drug interactions with the OTC drug, the label may be updated to include this information to help consumers avoid adverse reactions.
- Warning statements: The FDA may require the inclusion of more prominent or specific warning statements on the label to alert consumers to potential risks or adverse effects.
- Storage and handling instructions: Labeling changes can also address how the product should be stored and handled to maintain its safety and effectiveness.
- Product recalls or market withdrawals: In extreme cases, the FDA may require an OTC product to be recalled or withdrawn from the market due to serious safety concerns.

The regulatory process for safety-driven label changes on OTC medications in the United States, FDA involves several steps. An overview of the process is given below:

- Safety concern identification: The process usually begins when safety concerns arise. These concerns can be identified through various means, including adverse event reports, post-market surveillance, clinical studies, or emerging scientific evidence. Safety concerns may involve issues such as adverse reactions, side effects, drug interactions, inappropriate use, or inadequate warnings.
- Manufacturer's responsibility: OTC drug manufacturers are responsible for monitoring the safety and efficacy of their products. When a safety concern is identified, the manufacturer should promptly assess the information, perform necessary studies, and gather relevant data to understand the issue and its implications.
- Labeling changes proposal: If the manufacturer determines that a label change is necessary to address the safety concern, they will propose the changes to the FDA. The proposed label changes

should include revisions to the drug's labeling, such as warnings, precautions, contraindications, dosage instructions, or other information aimed at mitigating the safety risk.

- Submission to the FDA: The manufacturer submits the proposed label changes to the FDA for review and approval. This submission typically includes a comprehensive package of data and information supporting the need for the label change. The FDA reviews the submission to assess the proposed changes and their potential impact on public safety.
- FDA review and evaluation: The FDA's review of the proposed label changes is thorough and involves a multidisciplinary team of experts. They evaluate the scientific and clinical data provided by the manufacturer to determine whether the proposed changes adequately address the safety concern. The FDA may also consider input from external advisory committees, as needed.
- Communication with the manufacturer: Throughout the review process, the FDA maintains communication with the manufacturer to seek clarifications, request additional data or information, and address any concerns or questions.
- Approval or denial: Based on its evaluation, the FDA will decide to approve or deny the proposed label changes. If approved, the FDA may specify the exact wording and format for the new labeling. If denied, the FDA will provide the reasons for the denial.
- Implementation: Once the label changes are approved, the manufacturer is responsible for implementing the changes as soon as possible. This typically involves updating the product's labeling, including packaging, instructions, and promotional materials. The updated labeling is required to reflect the FDA-approved changes.
- Post-market surveillance: After the label changes are implemented, the FDA continues to monitor the safety and efficacy of the OTC medication through post-market surveillance, including the collection of adverse event reports and ongoing safety assessments.
- Public awareness: The FDA may issue public notifications, advisories, or safety alerts to inform healthcare professionals and consumers about the label changes and the reasons behind them.

The FDA's primary goal in this process is to ensure that OTC medications are safe and effective for use by the general public. Label changes are a critical tool for achieving this goal and providing consumers with the necessary information to use these products safely.

2. IMPLEMENTATION OF SAFETY RELATED LABELING CHANGES [SECTION 505(O)(4)] IN DRUG PRODUCTS PRESCRIBING INFORMATION UNDER FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT (FDAAA)

2.1. Identifying safety concerns[9]

Safety concerns about a medication can arise from various sources, such as adverse event reports, clinical trials, post-approval studies, peer-reviewed literature, or other relevant data. These concerns can be about serious risks or the evaluation of risk mitigation strategies.

2.2. Types of safety-related labeling changes (SrLC)

These changes usually involve updating sections of the medication's labeling, such as Boxed Warnings, Warnings and Precautions, Adverse Reactions, Contraindications, and Drug Interactions.

2.3. FDA's role in mandating label changes

The FDA can require label changes when there's significant safety information that needs to be addressed. This information may relate to risks associated with the medication, and it's typically mandated under Section 505(o)(4) of the FD&C Act.

2.4. Procedure for implementation of safety-related labeling changes (SrLC)

This is to assist applicants/holders of drug products in updating their labeling when the FDA notifies the applicants/holders to update the SrLC and the process flow is given in Figure 1.

2.4.1. Notification by the FDA to the applicant (s)

The FDA notifies the medication's manufacturer about the necessary safety-related labeling changes. This notification includes details about the safety information, recommended label modifications, and a timeframe for the response.

2.4.2. Response of the application holder (s)

The manufacturer has two options in response to the FDA's notification. They can submit proposed label changes or provide a detailed explanation if they believe changes aren't necessary (referred to as a rebuttal statement).

2.4.3. Evaluation of mandatory labeling supplement or rebuttal statement by the FDA[10-13]

The FDA reviews the submitted labeling supplements and rebuttal statements. They act quickly and may either approve the proposed changes or issue an order if there's a disagreement.

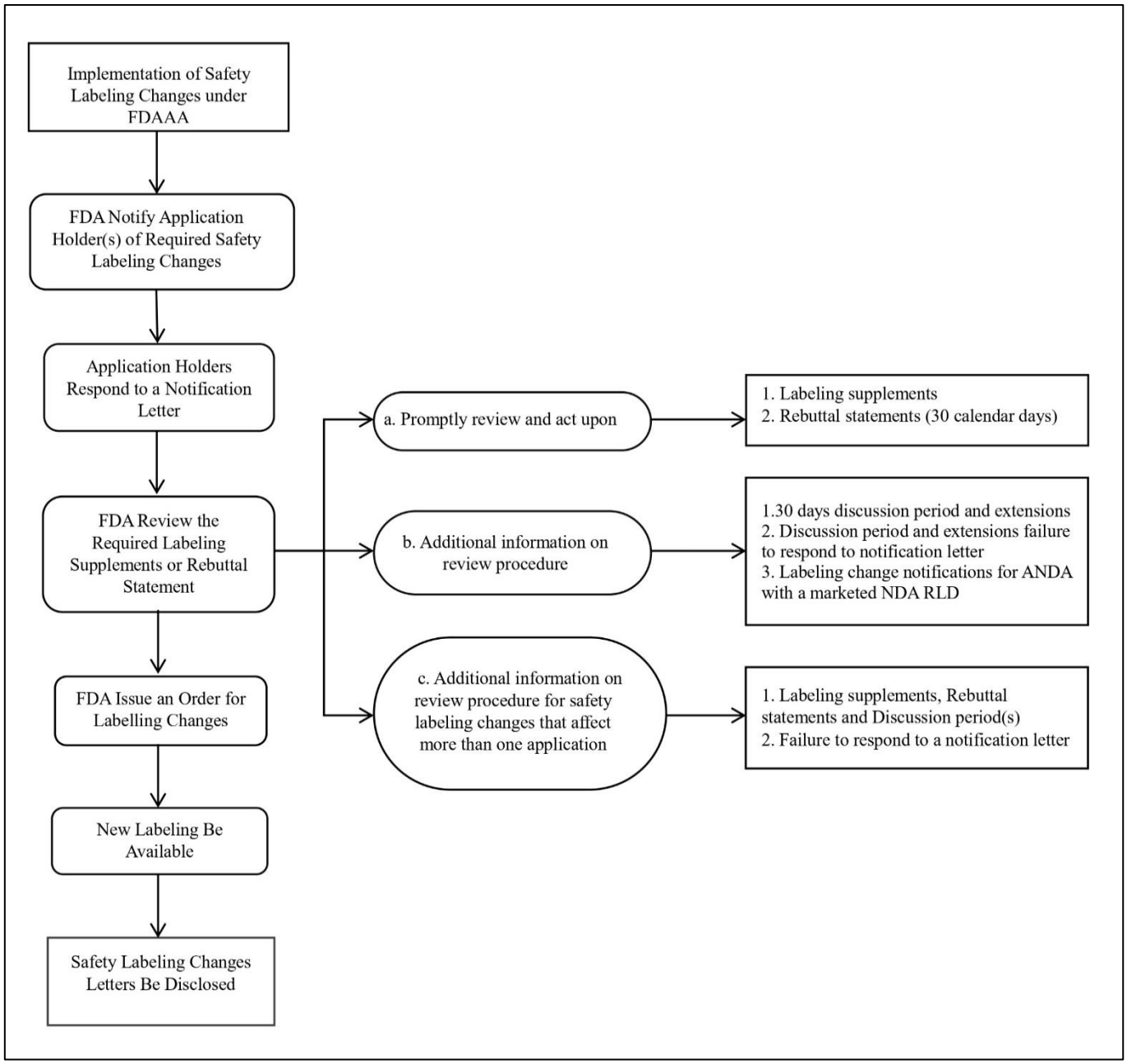

Figure 1. Flowchart for Implementation of (SrLC) [Section 505(o)(4)] under FDAAA.

2.4.3.1. Rapid review and action

This section outlines the FDA's process for quickly evaluating and responding to labeling supplements and rebuttal statements. There are two scenarios.

- Labeling supplement:
- When an applicant submits a labeling supplement, the FDA's review team promptly assesses it.
- They determine if the proposed language can be accepted as is or if further discussion is needed.
- If the FDA and the applicant agree on the proposed labeling changes, the FDA informs the applicant with a supplement approval letter.
- If there's disagreement, and a consensus can't be reached through discussions, the FDA has the authority to require the applicant to make the necessary labeling changes as specified in section 505(o)(4)(E).

- Rebuttal statement
- Similar to the process for supplements, when an applicant submits a rebuttal statement, the FDA review team quickly evaluates it.
- They assess whether the reasons provided by the applicant for not making labeling changes are acceptable.
- If the FDA and the applicant agree that labeling changes aren't needed, the FDA informs the applicant promptly.
- If there's a disagreement and no consensus is reached on the submission of a labeling supplement, the FDA can direct the applicant to make the required labeling changes, as stated in section 505(o)(4)(E).

2.4.3.2. Additional information on evaluation procedures

- 30-Day discussion periods and extensions
- According to section 505(o)(4)(D), the FDA can extend the discussion period beyond 30 days if necessary.
- An extension is usually granted when the initial period isn't sufficient to address all unresolved matters adequately.
- Situations that might warrant an extension include labeling changes for a drug class or significant revisions to supplement language.
- Before the initial 30-day discussion period ends, the FDA informs the applicant about the granted extension and provides an explanation if possible.
- Failure to respond to a notification letter
- If an applicant doesn't submit a labeling supplement or a rebuttal statement within 30 calendar days of receiving the notification letter, it's considered a relinquishment of the review and discussion period.
- As a result, the FDA can issue an order instructing the applicant to implement the required labeling changes.
- Notifications for abbreviated New Drug Applications (ANDAs) with a marketed New Drug Application (NDA) Reference Listed Drug (RLD).
- ANDA holders referencing a marketed NDA with an approved labeling supplement receive notifications from the Office of Generic Drugs (OGD) regarding necessary safety labeling changes.
- After receiving this FDA notification, ANDA holders must submit the required labeling changes within 30 days in a supplement known as changes-being-effected (CBE-0) in response to the written notification.

2.4.3.3. Additional information on evaluation for SrLC impacting multiple applications

- Labeling supplements, discussion period, and rebuttal statements.
- The approval process for labeling changes won't be delayed for other application holders in the same class if an order is issued to one or more holders.
- When there are class-wide labeling changes, the FDA sends approval or order letters to all relevant NDA, BLA, and ANDA holders without a marketed RLD on the same day.
- Failure to respond to a notification letter.
- In a group of applications, some holders may not respond to the notification letter within the designated 30-day period.
- However, the lack of response from these holders won't delay the approval of necessary Safety-related Labeling Changes (SrLC) for other application holders in the same class who do respond within the specified time limit.

2.4.4. Additional details on evaluation procedures

The FDA can extend the discussion period if needed. If no response is received within 30 days, the FDA may issue an order. For ANDAs referencing another application, ANDA holders are expected to make necessary changes within 30 days upon FDA notification.

2.4.5. Issuance of an order for labeling changes by the FDA

If the FDA determines that proposed changes are insufficient or if the manufacturer doesn't respond, an order for labeling changes may be issued. This is rare and involves discussions with senior managers.

2.4.6. Availability of new labeling[15]

The updated labeling should be available on the manufacturer's website within ten days of approval. The FDA also publishes approved updates on its website.

2.4.7. Disclosure of SrLC letters

Letters related to safety changes that apply to multiple applications are made public on the FDA's website for quick public communication. However, letters concerning a single application remain confidential, but the approved changes are posted on the FDA's website.

2.5. Supporting documents

The following documents should be provided in support of this change

- Form FDA 356h provided in Module 1.1.
- Cover letter provided in Module 1.2.
- A copy of the FDA's SLC notification letter provided in Module 1.2.
- The updated prescribing information (Word & PDF) provided in Module 1.14.1.3.
- The Medication Guide (Word & PDF) is provided in Module 1.14.1.3. (Only for those drug products that have standalone medication guide).
- The annotated comparison between the previously approved prescribing information and the proposed prescribing information is provided in Module 1.14.3.1.

3. REVISING ABBREVIATED NEW DRUG APPLICATION LABELING AS PER THE REFERENCE LISTED DRUG LABELING[16]

This is to assist applicants and holders of ANDA in updating their labeling when the approved labeling of RLD is revised and provides recommendations on how to identify updates in RLD labeling and how to submit

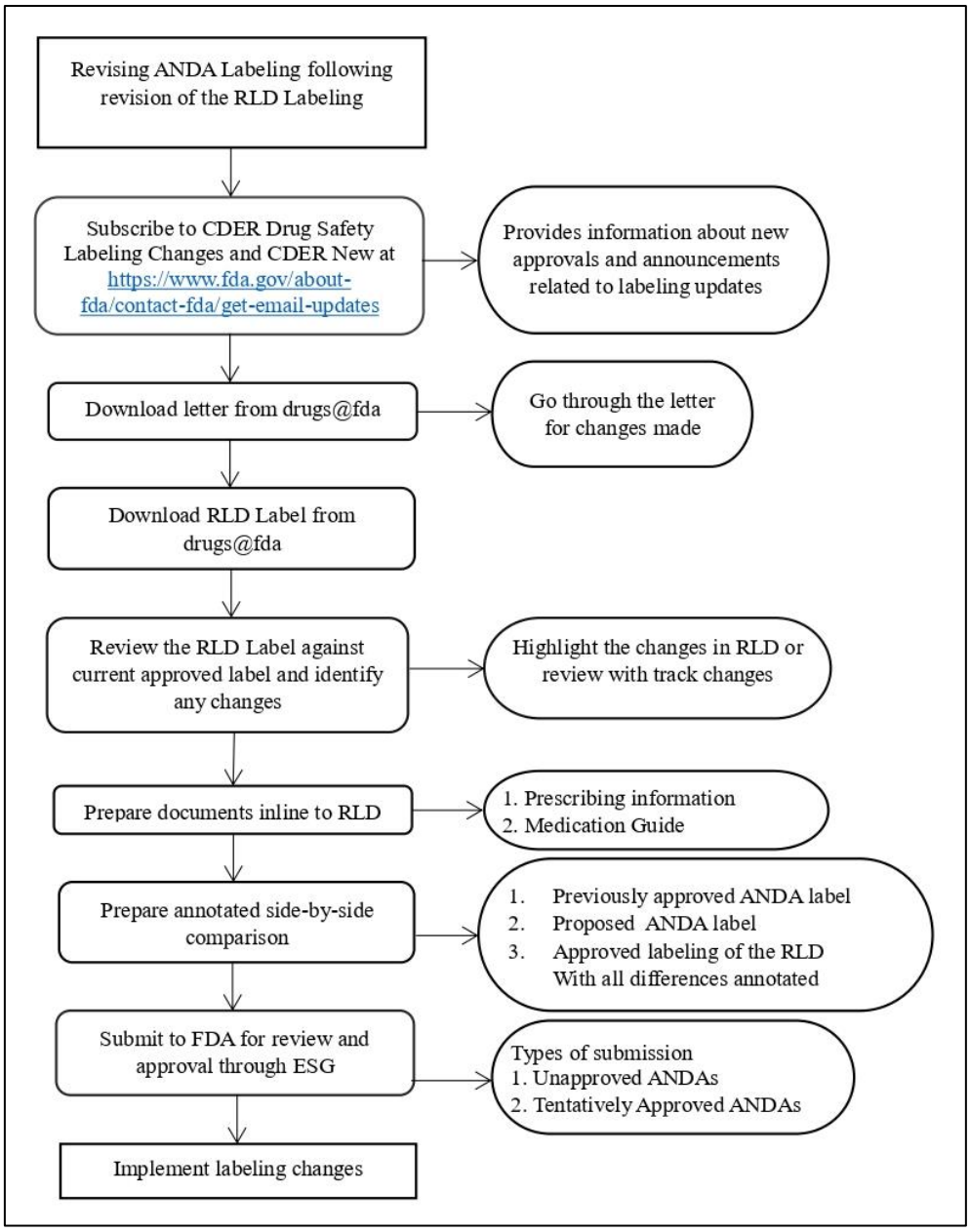

Figure 2. Updating Generic drug product prescribing information with reference to RLD.

amendments or supplements to update the labeling of ANDA and the process flow is given in Figure 2.

This given information emphasizes that all holders of marketing applications for drug products, including both NDA's and ANDA's, have a responsibility to ensure that their product labeling is accurate and not false or misleading. This means that they must proactively monitor and update their labeling when necessary.

Specifically, an ANDA holder is expected to update its labeling after the FDA has approved relevant changes to the labeling of the RLD. This ensures that the labeling of the generic drug remains consistent with the updated labeling of the RLD. By doing so, the ANDA holder ensures that their product remains in compliance with FDA regulations and continues to be safe and effective.

3.1. Procedure for updating ANDA label as per RLD label

3.1.1. Evaluate the impact of RLD label changes on the generic drug label

- Assess how the changes in the RLD labeling will impact the existing generic drug label.
- Identify specific sections or areas that need revision to ensure consistency and accuracy with the updated RLD label.
- Determine if any changes in the generic drug label are needed to align with the revised RLD labeling.

3.1.2. Preparation of labeling supplements[17]

- Develop labeling supplements that include the proposed changes to ANDA.

- Include supporting documentation, such as data, studies, or references, to justify the revisions.
- Ensure that the proposed changes align with the revised RLD labeling and are accurate and comprehensive.

3.1.3. Submission of labeling supplement to the FDA[18]

- Follow the FDA's submission requirements and guidelines for labeling supplements.
- Submit labeling supplements to the FDA.
- Ensure submission within the specified timeframe, typically within 30 days of the RLD label revision or as per FDA instructions.

3.1.3.1. Types of submission

The type of submission refers to how application holders of ANDA's should handle changes in labeling. Depending on whether ANDA is unapproved, tentatively approved, or approved, different procedures apply.

Unapproved ANDAs

If ANDA has not yet been approved, the applicant needs to make sure that the labeling of their generic drug matches the labeling of the RLD. Any changes required to align with the RLD labeling should be submitted as an amendment, following the FDA guidance for industry, ANDA Submissions – Amendments to Abbreviated New Drug Applications Under Generic Drug User Fee Act (GDUFA).

Tentatively approved ANDAs

If ANDA has received tentative approval, the applicant still needs to make sure that the labeling matches the RLD labeling. Any necessary changes should be submitted as an amendment to the tentatively approved application, following the FDA guidance for industry, ANDA Submissions - Amendments and Requests for Final Approval to Tentatively Approved ANDAs. It's important to submit these amendments in a timely manner to facilitate the final approval process based on patent and exclusivity protections.

Approved ANDAs

Once ANDA has been fully approved, the holder must ensure that their labeling remains consistent with any updates made to the labeling of the RLD, except for claims protected by patent and exclusivity. The FDA has specified different reporting categories for these updates, which should be followed as outlined in 21 CFR 314.70. Additional suggestions can be found in the FDA guidance for industry on Changes to Approved NDA or ANDA Submissions - Prior Approval Supplements under GDUFA.

3.1.4. Implement approved labeling changes[19]

Implement the approved labeling changes in a timely manner. Update the generic drug label to reflect the revised information in alignment with the RLD labeling changes.

The following documents should be provided in support of this change:

- Form FDA 356h provided in Module 1.1.
- Cover letter provided in Module 1.2.
- The updated prescribing information (Word & PDF) provided in Module 1.14.1.3.
- The Medication Guide (Word & PDF) provided in Module 1.14.1.3. (only for those drug products which have standalone medication guide)
- The annotated comparison between the previously approved prescribing information with the approved labeling of the RLD and the proposed prescribing information is provided in Module 1.14.3.1.

4. CONCLUSION

The regulatory framework for USFDA regulated drug product labeling updates is a comprehensive process that ensures accurate and up-to-date information is provided to healthcare professionals and patients. The prescribing information serves as a crucial source of information for medication use, including indications, dosages, contraindications, warnings, precautions, and adverse reactions.

The implementation of safety-related labeling changes (SrLC) under the FDAAA is an important aspect of the regulatory framework. The FDA identifies additional safety-related information through various sources and notifies the application holders about the required labeling changes. The application holders are then expected to respond by submitting proposed labeling changes or providing a detailed rebuttal statement if they believe a change is unnecessary.

The FDA evaluates the labeling supplements or rebuttal statements and takes appropriate actions. If there is agreement on the proposed changes, the FDA informs the application holder and approves the supplement. However, if there is disagreement, the FDA has the authority to require the necessary labeling changes.

The process also includes discussion periods, extensions if needed, and the ability of the FDA to issue orders for labeling changes. The FDA expects that issuing orders will be rare and involve discussions with senior managers.

Once the labeling changes are approved, the updated labeling should be made available on the applicant's website, and any approved updates will be published on the FDA's website. Notification letters regarding safety-related labeling changes that apply to multiple applications

are publicly disclosed to inform the general public about significant safety risks.

Overall, the regulatory framework ensures that the prescribing information is accurate, informative, and regularly updated to provide healthcare professionals and patients with the necessary information to make informed decisions about medication use. It reflects the FDA's commitment to patient safety and the importance of continuous monitoring and evaluation of medication risks and benefits.

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