

SOPP 8412: Review of Product Labeling

Version: 7

Effective Date: November 21, 2019

Table of Contents

I.	Purpose	1
II.	Scope.....	1
III.	Background	2
IV.	Definitions.....	6
V.	Policy.....	7
VI.	Responsibilities.....	9
VII.	Procedures.....	11
VIII.	Appendix	16
IX.	References	16
X.	History	18

I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for the review of labeling for human drug and biologic products, including combination products.

II. Scope

- A. This SOPP applies to the review of product labeling for drugs and biological products regulated under Biologics License Applications (BLA), New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA), and their respective supplements.
- B. This SOPP applies to the review of patient-oriented labeling that is submitted with human factors (HF) study protocols for combination products.
- C. This SOPP does not apply to labeling submitted in annual reports. Refer to *SOPP 8211.1: Administrative Handling and Review of Annual Reports for Approved Biologics License Applications (BLAs)* for procedures to be followed for labeling submitted in annual reports.

- D. This SOPP does not apply to medical devices, including IVDs regulated under BLA. Review of labeling for medical devices is covered in other device-specific SOPPs and/or Job Aids.

III. Background

- A. Proper labeling of licensed and approved products is a requirement of the Food, Drug and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act). Labeling is reviewed as part of a BLA, NDA, ANDA, their respective supplements, annual reports or product correspondence (First Use notification only), when appropriate, to ensure the information is correct and that the product is not misbranded.
- B. The mechanism for reporting changes to labeling varies according to the type of change and the change's potential for having an adverse effect on product identity, strength, quality, purity, or potency as described in 21 CFR 601.12 and 314.70. The reporting categories allowed by these regulations include several different administrative processes for labeling submission and review. For drugs and biologics subject to 21 CFR 314.70 and 601.12, respectively, changes to a product package label, container label, and package insert require either: (1) submission of a supplement with FDA approval needed prior to product distribution (Prior Approval Supplement (PAS)); (2) submission of a supplement with Changes Being Effected (CBE); or (3) submission of the final printed labeling in an annual report.
- C. On December 11, 2003, FDA published a Final Rule in the Federal Register (68 FR 69009 - the *Electronic Labeling Rule (ELR)*), requiring the submission of content of labeling in electronic format for marketing applications beginning June 8, 2004. The requirements of the rule can be found in 21 CFR 314.50(l)(1)(i) for NDAs, 314.94(d)(1)(ii) for ANDAs, 601.14(b) for BLAs and 314.81 (b)(2)(iii)(6) for annual reports. Following publication of the Final Rule, FDA issued *Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Content of Labeling* in April 2005. The publication of this guidance indicated that the electronic format by which content of labeling should be submitted is Structured Product Labeling (SPL), which utilizes Extensible Markup Language (.XML).
- D. On February 26, 2004, FDA published a Final Rule (69 FR 9120) requiring certain human drug and biological products to have on their labels a linear bar code that contains, at a minimum, the drug's National Drug Code (NDC) number (21 CFR 201.25). Refer to *Guidance for Industry: Bar Code Label Requirements Questions and Answers* (August 2011); this document also covers the requirements for machine-readable label requirements for blood and blood components. Refer also to *Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers* (September 2018) for additional information.

- E.** In January 2006, FDA issued a Final Rule (71 FR 3922 - the *Physician Labeling Rule (PLR)*), which required labeling for BLAs and NDAs to conform to 21 CFR 201.56 and 201.57 beginning June 30, 2006. For BLAs, NDAs, and efficacy supplements approved prior to June 2001, implementation of the PLR is voluntary. The PLR revised the existing labeling regulations to require that the prescribing information of new and recently approved human drug and biological products include a cross-referenced Highlights section and Table of Contents along with the Full Prescribing Information. It also established certain required content, the reordering of the label, and minimum format requirements. The intent of the PLR was to make the prescribing information more accessible and informative for practitioners to improve risk and benefit communications as well as risk management. Refer to *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013) for additional information.
- F.** In July 2006, the Institute of Medicine (IOM) published a report entitled *Preventing Medication Errors*, which cited labeling and packaging issues as the cause of 33 percent of medication errors. Product name confusion, as well as confusing packaging and labeling, contribute to these medication errors. Given the critical role of the label and prescribing information in the safe use of drug products, CBER relies on four major labeling reviews to ensure accurate information is provided in a manner understandable to physicians and patients. These reviews include the content of the prescribing information, the proper (established) name, the proprietary (trade or brand) name, and the format of carton and container labels.
- G.** A Circular of Information for the Use of Human Blood and Blood Components (the “Circular”) has been developed by the major industry organizations representing blood establishments and is reviewed by FDA to ensure compliance with 21 CFR 606.122. CBER announces in guidance that a particular version of the “Circular” is an acceptable standard and that it complies with the requirements and thereafter a copy of the Circular does not have to be submitted or reviewed with each submission if the accepted version is in use. After CBER’s announcement of acceptance of a Circular in a guidance document, firms may report the use of the accepted Circular in their annual reports if there are no changes made to the accepted version of the Circular.
- H.** On November 27, 2013, the Drug Supply Chain Security Act (DSCSA) was signed into law. The DSCSA amended the FD&C Act to include new requirements for the identification and tracing of certain prescription drugs as they are distributed within the United States. Section 582(b) of the FD&C Act requires that manufacturers affix or imprint a product identifier to each package and homogenous case of product intended to be introduced in a transaction into commerce. Under section 582(e) of the FD&C Act, repackagers must also comply with these requirements. The product identifier must be encoded with the product’s standardized numerical identifier, lot number, and expiration date. Under section 582(a)(9)(A), the product identifier data carrier format and

applicable data is specifically required to be included in a “2-dimensional data matrix barcode” for packages and in a “linear or 2-dimensional data matrix barcode” for homogenous cases. For more information, please refer to *Guidance for Industry: Product Identifier Requirements under the Drug Supply Chain Security Act – Compliance Policy*.

Although the labeling for most products will include a 2-dimensional data matrix barcode, in certain circumstances, a 2-dimensional data matrix barcode is not required under the statute, or an exception or exemption for such requirement may have been granted. Please contact the Office of Compliance and Biologics Quality if you have questions.

- I. In December 2014, FDA issued a Final Rule (79 FR 72064 - the *Pregnancy and Lactation Labeling Rule (PLLR)*), amending its regulations governing the content and format of the “Pregnancy,” “Labor and delivery,” and “Nursing mothers” subsections of the “Use in Specific Populations” section of the labeling for human prescription drug and biological products. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. For human prescription drug and biological products subject to the Physician Labeling Rule, the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The intent of the final rule was to create a consistent format to provide useful information about the risks and benefits of a prescription drug and/or biological product for prescribing decisions in pregnant women, in nursing mothers, and in females and males of reproductive potential. Refer to *Draft Guidance for Industry: Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products –Content and Format* (December 2014) for additional information.

1. Implementation Schedule:

Applications Required to Conform to New Pregnancy/Lactation Content Requirements (includes NDAs, BLAs and efficacy supplements)	Time by Which Labeling with New Pregnancy/Lactation Content Must Be Submitted to FDA for Approval
Applications submitted on or after effective date of final rule (June 30, 2015)	Time of Submission
Applications pending on the effective date of the final rule	4 years after the effective date of the final rule (June 30, 2019) or at the time of approval, whichever is later

Approved Applications Subject to the Physician's Labeling Rule:	Time by Which Labeling with New Pregnancy/Lactation Content Must Be Submitted to FDA for Approval
Applications approved any time from June 30, 2001, up to and including, June 29, 2002, and from June 30, 2005, up to and including June 29, 2007	3 years after the effective date of the final rule (June 30, 2018)
Applications approved any time from June 30, 2007, up to and including the effective date of the final rule	4 years after the effective date of the final rule (June 30, 2019)
Applications approved any time from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of the final rule (June 30, 2020)

2. For labeling not subject to the requirements of the PLR (i.e., applications approved prior to June 30, 2001), the pregnancy label category is required to be removed by three years after the effective date of the final rule (June 30, 2018).

IV. Definitions

- A. **Label** - Display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity (21 CFR 1.3(b)).
- B. **Labeling** - All written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce (21 CFR 1.3(a)). **Note:** Labeling includes the container labels, package insert (or professional labeling), the patient package insert, medication guides, instructions for use, risk management materials and promotional labeling.
- C. **Content of labeling** - All text, tables, and figures, such as contents of the package insert or professional labeling, patient package insert, and medication guide required under 21 CFR 201.100(d)(3). **Note:** The Physicians Labeling Rule (PLR) and the Pregnancy Labeling and Lactation Rule (PLLR) specify the format for the content of labeling.
- D. **Patient-oriented labeling** - Patient instructional materials that include only Instructions for Use (IFU) and Quick Reference Guides (QRGs).
- E. **Product Identifier** – A standardized graphic that includes the standardized numerical identifier, lot number, and expiration date of the product, in both human-readable and machine-readable formats. (See section 581(14) of the FD&C Act.)
- F. **Standardized numerical identifier** - A set of numbers or characters used to uniquely identify each package or homogenous case, composed of the NDC combined with a unique alphanumeric serial number of up to 20 characters. (See section 581(20) of the FD&C Act.)
- G. **First Use Notification:**
 1. Final Printed Labeling – SPL version of label or labeling (carton and container and accompanying matter) available immediately upon marketing of the product and submitted to CBER as product correspondence or in an annual report.
 2. Final Content of Labeling - All text, tables, and figures, such as contents of the package insert or professional labeling, patient package insert, and medication guide required under 21 CFR 201.100(d)(3) submitted in

electronic format (Final SPL) and submitted to CBER as product correspondence. (21 CFR 601.14)

H. Structured Product Labeling (SPL) - The electronic format by which content of labeling should be submitted. SPL utilizes Extensible Markup Language (.XML).

V. Policy

- A.** SPL formatted content of labeling (.XML file) and a Microsoft (MS) Word-formatted version (.docx file) should be submitted with original BLA/NDA/ANDA submissions, efficacy supplements, and all supplements that require review of labeling. An MS Word version is not required for changes reported in an annual report or for human blood and blood component products using an Instruction Circular.
- Labeling negotiations for original and supplemental BLA/NDA/ANDA submissions are performed using the track changes (redline/strikeout) function in MS Word. Note: there may be instances that require explanatory text or separate annotation within the document or as a separate document.
 - A revised SPL is not required during the labeling negotiations.
 - SPL can accommodate both PLR/PLLR and non-PLR/PLLR formats, Medication Guides, Patient Package Inserts (PPIs) and Instructions for Use.
- B.** Labeling revisions are subject to the provisions under FDAAA Section 901 for Safety Labeling Changes and FDAAA Section 501 for the Pediatric Research Equity Act (PREA).
- C.** Under section 582(a)(8) of the FD&C Act, changes made to package labels solely to incorporate the product identifier may be submitted in the annual report of an establishment.
- D.** Labeling submitted in annual reports are only those types of changes outlined in 21 CFR 314.70(d) or 21 CFR 601.12(f)(3). These are usually minor/editorial-type labeling changes. Annual reports will be handled in accordance with *SOPP 8411.1: Administrative Handling and Review of Annual Reports for Approved Biologics License Applications (BLAs)*.
- E.** For human blood and blood component products, a revised instruction Circular should be submitted in the following situations:
1. A firm may modify the "Circular" to contain facility specific information or to include additional products or cautions announced by the FDA. Depending on the type of information added, the submission of a modified Circular of Information may be a PAS, CBE or annual report.

2. When a firm submits a supplement for a new product and provides an instruction circular or indicates that the “Circular” has been modified, the submission is categorized as a PAS. CBER review of the circular is to ensure the content is in compliance with the regulations or that the modified “Circular” is consistent with the accepted standard Circular of Information. Any modifications requiring additional review are identified. See *Guidance for Industry: An Acceptable Circular of Information for the Use of Human Blood and Blood Components*.
- F. At the time of First Use (at time of distribution or sale), the applicant must submit the following as product correspondence or in an annual report if its submission coincides with distribution:
1. Final content of labeling (21 CFR 601.14) in SPL format, and may include electronic rendering/images (.jpeg) of cartons and containers.
 2. Final advertising and promotional labeling at the time of initial dissemination or publication, on Form FDA 2253 (21 CFR 601.12(f)(4)).
- G. For multiple supplements that include labeling revisions under review for the same product/same applicant, a coordinated review of all submitted label changes should be conducted to ensure coordination with all open submissions and include language of recently approved versions.
1. Upon receipt of approved language from a CBER review committee, the newly approved language will be reviewed by other affected review committees to determine whether or not that language will impact their review.
 2. Labeling coordination should be performed by a Regulatory Project Manager (RPM).
- H. Pending CBE safety language should not be included in another pending labeling supplement until after CBE approval. The RPM should make review committees for the same product/same applicant aware of pending safety information under review. The purpose of notification is to make review committees aware of pending safety information for consideration in their review.
- I. Labeling revision requests to the applicant should be as complete as possible. The applicant is responsible for revising and resubmitting proposed labeling for review if labeling revisions are necessary.
- **Note:** An SPL file may include changes approved in more than one submission. Any approval to revised content of labeling must be reflected in all other open submissions (i.e., applicants of open labeling supplements should be asked to update the proposed labeling in an amendment). Thus, at any given time, the SPL that is approved (and posted publicly) reflects the

most inclusive and up-to-date content of labeling. Refer to Regulatory Job Aid *JA 900.02: SPL Content of Labeling* for additional information.

VI. Responsibilities

A. Review Committee

1. Participates in the labeling review to ensure compliance with the content and formatting requirements per applicable regulations.
2. Provides comments as appropriate in review memorandum.

B. Regulatory Project Manager (RPM)

1. Facilitates, as necessary, the coordination of label and labeling review activities, such as ensuring assignment of appropriate discipline committee members, scheduling labeling meetings, communication with the applicant, etc.
2. Coordinates review of multiple pending supplements that include labeling revisions to ensure approved labeling includes all recently approved labeling revisions, as applicable.
3. Serves as the primary point-of-contact with the applicant. The RPM should be included in all communications with the applicant.
4. Ensures all bar code information submitted by an applicant is reviewed by appropriate reviewers.
5. Ensures National Drug Code (NDC) assignment(s) is accurate. See Regulatory Job Aid *JA 900.08: National Drug Code and Bar Code and Product Identifier Labeling Review* for additional information.

C. Clinical Reviewer

1. Ensures accuracy of clinically relevant product information in the labeling and compliance with content requirements, i.e., PREA, PLR, PLLR, and all labeling regulations (see comprehensive list in the references section).
2. Coordinates labeling issues during a review.
3. Evaluates the Advertising and Promotional Labeling Branch (APLB) recommendation for Proprietary Name Review (PNR). Includes evaluation supporting or disagreeing with APLB recommendation for the proprietary name in the clinical review memo.

D. Statistician

Evaluates the accuracy of statistical clinical data included in the prescribing information relative to the information provided in the submission.

E. Clinical Pharmacology Reviewer

Ensures accuracy of mechanism of action statements, pharmacodynamics, pharmacokinetics, and information on the impact of age, gender, and race in the labeling.

F. Non-Clinical Toxicologist Reviewer

Ensures accuracy of non-clinical toxicology product information relative to information provided in the labeling.

G. Chemistry Manufacturing and Control (CMC) Reviewer

1. Ensures accuracy of chemistry and manufacturing product information relative to the information provided in the labeling (storage conditions, suitable expiry periods established, etc.).
2. Reviews UNII (Unique Ingredient Identifier) Code request, in collaboration with FDA's Substance Registration System (SRS), and concurs with the recommendation as appropriate. See Regulatory Job Aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.
3. Ensures that the UNII codes and drug listing data elements in the SPL file are correct.
4. Ensures all bar code information submitted by an applicant is reviewed by appropriate reviewers.
5. Ensures NDC assignment(s) is accurate. See Regulatory Job Aid *JA 900.08: National Drug Code and Bar Code and Product Identifier Labeling Review* for additional information.

H. Advertising and Promotional Labeling Branch (APLB) Reviewer

1. Performs Proprietary Name Review (PNR), preparing a review memorandum that includes consultation with the clinical reviewer and/or chair.
2. Provides consult to the clinical reviewer and/or chair on the content of the prescribing information labeling from a comprehension and readability perspective, ensuring that the labeling is not false or misleading to the target audience(s) (i.e., healthcare providers, patients, special populations) and ensuring consistency with the labeling regulations.
3. Reviews labels and labeling for false or misleading promotional claims and representations.

VII. Procedures

A. General Information

1. Not all process steps outlined below apply to labeling reviews associated with human blood and blood component products. Refer to the following regulatory job aid for additional information: *JA 910.05: Labeling Review for Whole Blood and Blood Components including Source Plasma and Source Leukocytes*.
2. Please refer to the following regulatory job aid for additional information regarding labeling reviews conforming to requirements (as of June 30, 2015) for sections 8.1 through 8.3 of the full prescribing information: *JA 910.14: Labeling Review- Pregnancy, Lactation and Females and Males of Reproductive Potential*.
3. Reviewer tools are available on the FDA Intranet.
4. SPL resources are available on the Internet.
5. Additional/companion submissions containing labeling may be found by searching the RMS-BLA database. See Regulatory Job Aid *JA 910.03: RMS-BLA Database Search for Labeling Submissions*.
6. For information regarding labeling changes related to the issuance or reissuance of Biological Products Licenses refer to *SOPP 8403: Issuance and Reissuance of Licenses for Biological Products*.

B. Original BLA/NDA/ANDA and Efficacy Supplements

1. Initial processing [refer to *SOPP 8401: Administrative Processing of Biologics License Applications (BLAs) and New Drug Applications (NDAs)*]:
 - a. Verify labeling (i.e. content of prescribing information, carton, and container labels) has been submitted, including an SPL (.XML) file and a MS Word (.docx) version, if applicable. **[RPM]**
 - b. Request reviewer assignments for clinical, statistics, clinical pharmacology, toxicology, CMC, and APLB, and others as applicable. **[RPM]**

Note: A clinical reviewer and an APLB reviewer are included on all submissions containing labeling revisions.
2. Examine all labeling components and note any missing information at the Filing Meeting. **[Review Committee Members]**

3. Determine the planned target date for communication or feedback regarding labeling to the applicant and include date in the Filing Letter. **[Review Committee Members]**
4. For Proper (Established) name review, ensure compliance with naming conventions as established by US Adopted Name Council (USAN) or office-specific policies if no USAN name is available according to *SOPP 8426: Assignment of Biological and Drug Product Proper Names and Biological Suffixes*. **[RPM or designee]**
5. Confirm submission of the Proprietary Name Review (PNR) request in the application, record the proposed proprietary name in the appropriate regulatory database, and if PDUFA product, confirm PDUFA milestone data entry per *JA 910.02: Proprietary Name Review (PNR) Processing*. **[RPM]**
6. Review proprietary name to ensure compliance with the regulations, document recommendation in a review memorandum, communicate findings to applicant and document in appropriate databases according to *SOPP 8001.4: Review of Proprietary Names for CBER Regulated Products* and *JA 910.02: Proprietary Name Review (PNR) Processing*. **[APLB Reviewer, Product Office Designee, RPM]**
7. Ensure Unique Ingredient Identifier (UNII) Code request is processed in accordance with *JA 900.01: Unique Ingredient Identifier (UNII) Code*. **[RPM, CMC reviewer]**
8. Ensure compliance with labeling requirements as described in 21 CFR Parts 201, 202, 606, 610, 640 and 660, as applicable. **[Review Committee Members]**
9. Review labeling from a promotional, comprehension and readability perspective, including consideration of potential medication errors due to content and format issues. **[APLB Reviewer]**
10. Ensure compliance with promotional labeling and advertising requirements as described in 21 CFR Part 202, *Prescription Drug Advertising*. **[APLB Reviewer]**
11. Ensure accuracy of NDC and bar code information. **[RPM, CMC Reviewer]**
12. Hold labeling meeting(s) after mid-cycle to discuss proposed labeling revisions. **[Review Committee]**
 - a. Complete a thorough review of the labeling before the labeling meeting. **[Review Committee Members]**

- b. Provide a draft clinical memorandum to the APLB reviewer to allow for the completion of the APLB Labeling Review memorandum. **[Clinical Reviewer]**
 - c. Provide a formal APLB Labeling Review memorandum to the clinical reviewer, committee chair, and RPM with labeling revision recommendations based on the clinical review and labeling discussions, as appropriate. **[APLB reviewer]**
 - Additional consults with APLB are available on a case-by-case basis thereafter but output that results from these further consultations may not be provided in an additional formal memorandum. These additional comments may be conveyed via meeting minutes, telecon minutes, or email communications.
 - d. Collaboratively identify labeling requirements/revisions. **[Review Committee Members]**
 - e. Summarize labeling issues identified at this meeting for inclusion in the Summary Basis of Regulatory Action (SBRA), as appropriate. **[Committee Chair, RPM]**
13. Communicate labeling revision(s) to the applicant. Communications may include any revision requests previously communicated but not already addressed (i.e. Filing Letter, etc.). **[RPM]**
- a. This communication may occur anytime during the review; however, it most commonly occurs after the labeling meeting.
 - b. If needed, labeling meeting(s) may be held with the applicant to resolve labeling disagreements or provide clarification. **[Review Committee]**
14. Upon receipt of draft labeling revised as a result of labeling negotiations, confirm changes are consistent with requested changes. **[RPM]**
15. Document in the review memorandum any labeling issues that should be identified in the SBRA. **[Review Committee Members]**
16. Notify applicant of acceptance of proposed draft labeling and request applicant to submit an amendment to the application that contains the final draft labeling. The date of the final draft approved accepted labeling is identified in the approval letter or attached to the approval letter (only for whole blood and blood components or source plasma). **[RPM]**
- a. If approval is imminent with insufficient time to submit a formal amendment,

- i. Request that applicant provide agreed upon labeling via secure email or fax with agreement to submit labeling in a formal amendment within 2 weeks.
- ii. Advise applicant to provide assurance that labeling submitted in the amendment is identical to labeling provided via email/fax.
- iii. Document as a telephone conversation in the EDR.

17. Ensure that the "Post to Web" checkbox in RMS-BLA is completed so that the approved final draft labeling is included in the Action Package for Posting (see *SOPP 8401.7: Action Package for Posting*). **[RPM]**

C. Labeling Changes Submitted After Approval of Original BLA/NDA/ANDA (21 CFR 314.70 and 601.12)

1. Determine if the proposed labeling change is classified under the correct change category and verify that manufacturer's name is correct/has not changed (e.g., PAS, CBE, annual report). **[Review Committee Members]**
 - a. Promptly notify the applicant by telephone and letter, if the category is incorrect, and inform them of the correct category. **[RPM]**
 - b. Notify DMPQ if name change is identified. **[RPM]**
 - c. Request reviewer assignments, as applicable, for clinical, statistics, clinical pharmacology, toxicology, CMC, and APLB. **[RPM] Note:** An APLB reviewer should be included on all submissions containing labeling revisions.
 - d. Provide submission link to the review committee along with a list of associated submissions that have open labeling for review. Additional/companion submissions with labeling may be found by searching the RMS/BLA database. See *JA 910.03: RMS-BLA Database Search for Labeling Submissions*. **[RPM]**
2. Ensure the submission includes an SPL that reflects currently approved labeling in addition to the requested change for that submission. **[RPM]**
 - **Note:** Pending CBE safety language should not be included in another pending labeling supplement until after CBE approval. The RPM should make review committees for the same product/same applicant aware of pending safety information under review. The purpose of notification is to make review committees aware of pending safety information for consideration in their review.
3. Perform a comparison to the previous version of changes to approved labeling received in SPL format and document any differences. Refer to

- Regulatory Job Aid *JA 900.09: SPL Comparison Instructions* for additional information. **[RPM]**
4. Communicate concerns raised during labeling comparison with applicant. **[RPM]**
 5. Ensure UNII Code request is processed in accordance with *JA 900.01: Unique Ingredient Identifier (UNII) Code*. **[RPM, CMC reviewer]**
 6. Ensure compliance with labeling requirements as described in 21 CFR Parts 201, 202, 606, 610, 640 and 660, as applicable. **[Review Committee Members]**
 7. Review labeling from a promotional, comprehension and readability perspective, including consideration of potential medication errors due to content and format issues, as applicable, for example if there are changes to how used or patient use information. **[APLB Reviewer]**
 8. Ensure accuracy of NDC and bar code information. **[RPM, CMC reviewer]**
 9. Communicate labeling revisions to the applicant. Communications may include any revision requests previously communicated but not already addressed. **[RPM]**
 - a. This communication may occur anytime during the review.
 - b. If needed, labeling meeting(s) may be held with the applicant to resolve labeling disagreements or provide clarification. **[Review Committee Members]**
 10. Upon receipt of draft labeling revised as a result of labeling negotiations, confirm changes are consistent with requested changes. **[RPM]**
 11. Research concurrent open submissions with labeling for review to ensure coordination with all open submissions. **[RPM]**
 12. Notify the review committee(s) of any pending supplements for the same product/applicant so that the newly approved version of the labeling can be requested from the applicant, if the applicant does not amend the submission to include the newly approved labeling. **[RPM]**
 13. Notify applicant of acceptance of proposed draft labeling and request applicant to submit an amendment to the application that contains the final draft labeling. The date of the final draft approved labeling will be identified in the approval letter or attached to the approval letter (only for whole blood and blood components or source plasma). **[RPM]**

- a. If approval is imminent with insufficient time to submit a formal amendment,
 - i. Request that applicant provide agreed upon labeling via secure email or fax with agreement to submit labeling in a formal amendment within 2 weeks.
 - ii. Advise applicant to provide assurance that labeling submitted in the amendment is identical to labeling provided via email/fax.
 - iii. Document as a telephone conversation in the EDR.

VIII. Appendix

A. N/A

IX. References

A. References below are CBER Internal:

1. CBER Regulatory Job Aids:

- a. 900.01: Unique Ingredient Identifier (UNII) Code
- b. 900.02: SPL Content of Labeling
- c. 900.08: National Drug Code, Bar Code and Product Identifier Labeling Review
- d. 900.09: SPL Comparison Instructions
- e. 910.02: Proprietary Name Review (PNR) Processing
- f. 910.03: RMS-BLA Database Search for Labeling Submissions
- g. 910.05: Labeling Review for Whole Blood and Blood Components including Source Plasma and Source Leukocytes
- h. 910.14: Labeling Review - Pregnancy, Lactation and Females and Males of Reproductive Potential

B. References below can be found on the Internet:

1. [21 CFR](#)

Relevant sections are: Parts §201, §201.10(c), §201.56, §201.57, §201.80, §201.100(d)(3), §202.1, §299.4, §314.50(l)(1)(i), §314.70, §314.81 (b), §314.94(a)(8), §601.12, §601.14(b), §610, §606,122, 640.84, 640.94 and 660.28

2. [Electronic Submissions Web Page](#)
3. Legislation:
 - a. [Food and Drug Administration Amendments Act \(FDAAA\), September 2007](#)
 - b. [Prescription Drug User Fee Act \(PDUFA\)](#)
 - c. [Pediatric Research Equity Act \(PREA\) December 2003](#)
 - d. [Drug Supply Chain Security Act \(DSCSA\)](#)
4. [Federal Register:](#)
 - a. Content and Format of Labeling for Human Prescription Drugs and Biological Products, Requirements for Pregnancy and Lactation Labeling (commonly referred to as the Pregnancy and Lactation Labeling Rule [PLLR]), December 2014. 79 FR 72064
 - b. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, (commonly referred to as the Physician Labeling Rule [PLR]), January 2006. 71 FR 3922
 - c. Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format (commonly referred to as the Electronic Labeling Rule); December 2003. 68 FR 69009
 - d. Bar Code Label Requirements for Human Drug Products and Biological Products; Final Rule; February 26, 2004 (Volume 69, Number 38). 69 FR 9120
5. [Prescription Drug Labeling Resources](#)
6. Guidances:
 - a. [Guidance for Industry: Providing Regulatory Submissions in Electronic Format- Content of Labeling](#)
 - b. [Guidance for Industry: An Acceptable Circular of Information for the Use of Human blood and Blood Components](#)
 - c. [Guidance for Industry; Contents of a Complete Submission for the Evaluation of Proprietary Names](#)
 - d. [Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements](#)

- e. [Draft Guidance for Industry: Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format](#)
 - f. [Guidance for Industry: Product Identifier Requirements under the Drug Supply Chain Security Act – Compliance Policy](#)
 - g. [Guidance for Industry: Bar Code Label Requirements Questions and Answers](#)
 - h. Draft [Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers](#)
7. SOPPs:
- a. [SOPP 8001.4: Review of Proprietary Names for CBER Regulated Products](#)
 - b. [SOPP 8401: Administrative Processing of Original Biologics License Applications \(BLA\) and New Drug Applications \(NDA\)](#)
 - c. [SOPP 8401.7: Action Package for Posting](#)
 - d. [SOPP 8403: Issuance and Reissuance of Licenses for Biological Products](#)
 - e. [SOPP 8411.1: Administrative Handling and Review of Annual Reports for Approved Biologics License Application \(BLAs\)](#)
 - f. [SOPP 8426: Assignment of Biological and Drug Product Proper Names and Biological Suffixes](#)

X. History

Written/Revision	Approved	Approval Date	Version Number	Comment
Monser	Reviewed by Job Aid Coordinator	November 21, 2019	7	Technical Update to correct hyperlinks and typographical errors, update references and update to current format/font.

Monser	Chris Joneckis, PhD	June 17, 2018	6	Revised to remove request for paper copies of carton/container labeling, to add DSCSA info, to cover POL/IFU and updated throughout
Monser, LSC	Chris Joneckis, PhD	Jan 18, 2016	5	Revised to include Pregnancy and Lactation Labeling Rule
Dixon, Perkins	Robert Yetter, PhD	March 21, 2012	4	Revised to include Bar Code information
Rehkopf/RMCC	Robert Yetter, PhD	Oct 13, 2011	3	Update to new format and processes
L. Falk/RMCC	Robert, Yetter, PhD	Mar 20, 2008	2	Update to include Physician's Labeling Rule; Submission of labeling in Structured Product Labeling Format
	Robert Yetter, PhD	Dec 23, 2002	1	Original version of SOPP