Guidance for Industry

SPL Standard for Content of Labeling Technical Qs & As

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Electronic Submissions
Revision 1

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INTRODUCTION

This guidance is intended to assist applicants who submit content of labeling to FDA as part of a marketing application using the structured product labeling standard (SPL) in extensible markup language (XML). The guidance also provides information to FDA staff who review and manage product information using electronic systems. This is revision 1 of a guidance of the same name that was issued in December 2005. The guidance has been revised to reflect changes in the technology since 2005 and to harmonize the submission of SPL in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). We anticipate that additional guidance will be provided as new questions arise about the use of SPL in different contexts.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

BACKGROUND

In the *Federal Register* of December 11, 2003 (68 FR 69009), FDA published final regulations requiring that the content of labeling be submitted to FDA electronically for new drug

[1] This guidance has been prepared by Office of Critical Path Programs in the Office of the Commissioner at the Food and Drug Administration.

[2] See FDA's guidance *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing.*

applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs),[3] and annual reports (see 21 CFR 314.50(l), 314.94(d), 601.14(b), and 314.81(b), respectively). The regulations state that the content of labeling must be submitted to FDA electronically and "in a form that FDA can process, review, and archive."

Initially, CDER accepted electronic submissions of content of labeling in portable document format (PDF). Then, in September 2004, CDER announced that it would accept content of labeling in both PDF and SPL formats until the autumn of 2005, when PDF would be eliminated. On October 21, 2005, CDER announced in public docket number 92S-0251 that effective October 31, 2005, CDER would no longer accept content of labeling submissions in PDF format and that applicants should use the SPL standard when submitting content of labeling to FDA in XML with original submissions, supplements, and annual reports. CBER made a similar announcement on July 11, 2008, that went into effect on October 15, 2008. In a Draft Guidance that published on July 10, 2008, CDER, CBER and the Center for Veterinary Medicine announced their intention to begin using the SPL standard for electronic drug establishment registration and drug product listing (a final version of that guidance was issued at the end of May 2009).

Since FDA began accepting content of labeling in SPL format for application submissions, we have received numerous questions about SPL submission requirements. Based on preliminary questions, and in an effort to provide easy access to the answers to frequently asked questions, in December 2005, we published the first guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*. In an effort to provide the most useful and up-to-date information on SPL submissions, FDA is revising the December 2005 guidance. The revision provides both updated answers to questions previously addressed and information responsive to other questions related to submissions in SPL format. The Agency plans to continue updating this guidance with additional answers to questions as warranted.

For definitions of SPL-related terms, please see FDA's Data Standards Council Web site at www.fda.gov/oc/datacouncil. If you have additional questions about SPL submissions, you should contact spl@fda.hhs.gov. For questions on submissions to CDER or CBER, contact the appropriate electronic submission coordinator at esub@cder.fda.gov or esubprep@cber.fda.gov, respectively. Specific questions pertaining to content of labeling should be directed to the relevant review division or office in the appropriate center.

[3] The final regulations do not apply to devices regulated under a BLA.

TECHNICAL QUESTIONS AND ANSWERS

1. What was the implementation date for using the SPL for content of labeling in FDA application submissions?

For CDER-regulated products, the implementation date was October 31, 2005. For CBER-regulated products, the implementation date was October 15, 2008.

2. When do I need to include an SPL file in my submission?

An SPL file must accompany all submissions that propose changes to the content of labeling, including certain amendments (e.g., an amendment to a "changes being effected" (CBE) supplement containing updated content of labeling), submissions of final approved content of labeling (regardless of marketing date), and annual reports (see question 34 for more information on annual reports).[4]

3. What if I have already submitted SPL content of labeling during the registration and listing process?

This guidance only applies to SPL files submitted with applications. Additional guidance has been drafted that applies to the registration and listing process.[5] If you have already submitted identical content of labeling in a SPL file during the registration and listing process, you need not include the SPL file in your application. Instead, we recommend that you update your application by referencing the SPL file in the registration and listing system. To do this, place a link in your application submission that directs FDA to your SPL file (e.g., "We have submitted the SPL file with drug listing; it can be found at the following location http://www.accessdata.fda.gov/spl/data/ [*insert your SPL document id root here/insert SPL document id root here*].xml"] (see also question 31)."

The SPL document ID has to be repeated in the URL for the users to be able to access the SPL files from the Web server location.

4. Do other labeling documents need to be provided using the SPL standard?

No. Only electronic *content of labeling* is to be submitted using the SPL standard (including the XML document and all associated image files referenced in the XML document, such as chemical structures or graphs included in a clinical studies section). Other labeling documents (e.g., the annotated labeling, container labels, and carton labels) should not be submitted to the application using the SPL standard.

[4] See 21 CFR 314.50(l) for NDAs, 314.94(d) for ANDAs, 601.14(b) for BLAs, and 314.81(b) for annual reports.

[5] See FDA's guidance *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing*.

5. Should an applicant still submit an annotated Word version of the content of labeling?

Yes. We recommend that applicants continue to submit the annotated Word version of the label and all labeling for the product. SPL is the current standard for electronic content of labeling submissions and replaces proposed content of labeling submissions in PDF format.

6. How do I send my SPL file to FDA when making an electronic submission?

The SPL file should be included in a folder marked *spl* within the labeling folder. Refer to guidance for industry *Providing Regulatory Submissions in Electronic Format – Content of Labeling* for more information on the SPL submission process.

Alternatively, you can provide the Uniform Resource Locater (URL) to the SPL file for CBEs, annual reports, and final approved labeling if the SPL labeling was already submitted during the electronic registration and listing process.

7. How do I send my SPL file to FDA if my submission is in paper format?

When accompanying a submission in paper format, the SPL file should be submitted using electronic media (e.g., CD-ROM). The SPL should be included in a folder marked *spl* (see guidance for industry *Providing Regulatory Submissions in Electronic Format – Content of Labeling*).

8. Where do I send my SPL submission?

For products regulated by CDER, see http://www.fda.gov/cder/regulatory/ersr/default.htm, for the address to send electronic submissions. For products regulated by CBER, see http://www.fda.gov/CBER/regsopp/8110.htm. Consult www.fda.gov/esg for submissions via the Electronic Submissions Gateway for both CDER and CBER regulated products.

9. When did CDER and CBER begin accepting SPL for content of labeling?

CDER began accepting content of labeling in SPL format in September 2004. At that time, CDER accepted content of labeling submissions in both SPL and PDF and announced that CDER would begin accepting only SPL beginning in the autumn of 2005. Since October 31, 2005, CDER has been accepting content of labeling submissions only in SPL format. CBER began accepting content of labeling exclusively in SPL format on October 15, 2008, as noted in the memorandum to the electronic submissions docket, published on July 11, 2008.

10. Should ANDA applicants wait for submission of content of labeling for the reference listed drug (RLD) before they submit content of labeling in SPL format?

No. If an ANDA applicant determines that content of labeling has not been submitted in SPL

format for the reference listed drug, the ANDA applicant should still submit its own content of labeling in SPL format.

11. Can the electronic labeling be submitted under separate cover and cross-referenced to a paper submission for all types of submissions, including new ANDAs, supplements, and annual reports, or should the entire submission be done electronically?

Yes, a combination of electronic labeling for the content of labeling and paper application submission would be appropriate.

12. Does the SPL content of labeling replace the 12 copies of paper labeling, also known as final printed labeling (FPL), that are normally submitted with an application?

The requirement under 21 CFR 314.50 (l)(i) to provide content of labeling in electronic form is in addition to the obligation to submit copies of the label and all labeling, including 12 paper copies of FPL, as required by section 314.50(e)(2)(ii) . See also 314.94(d)(i)(ii) (ANDAs) and 601.14(b)(2) (BLAs). Applicants should submit either 12 paper copies or 1 PDF copy of FPL carton and container labels, but should submit only SPL files for the content of labeling submitted with an application.

13. If the content of labeling is approved based on the draft SPL, when should the final SPL be submitted after approval?

The final SPL should be submitted preferably within 14 calendar days after approval or as soon as possible thereafter.

14. Can we e-mail SPL to the Agency?

No. SPL should be submitted either to FDA's Electronic Document Room with documentation appropriate for the type of electronic submission or during the registration and listing process (see response to Question 7).

15. Should I submit content of labeling in Word and/or PDF with the SPL?

You should no longer submit content of labeling in PDF. However, we recommend that you continue to submit content of labeling in Word. The Word files facilitate the exchange of labeling comments and revisions between the applicant and FDA.

16. Where should I submit SPL files if the application contains both paper and electronic components?

Both components of the application should be sent to the relevant center's central document room (just as before implementation of SPL). Similarly, as before implementation of SPL, the staff will upload the electronic component.

17. Should companies resubmit labeling in SPL if it was submitted before October 15, 2008, in another format and is currently under review in CBER?

No, but we recommend that applicants work with the individual review division or divisions to ensure that SPL is available within a reasonable time frame for those products with submissions before October 15, 2008.

18. Can FDA refuse to file my submission if I do not provide SPL, given that I am required to do so?

Yes, but we will work with you to help you submit the SPL.

19. What software do I use to create SPL files?

An SPL file can be created using a variety of tools, ranging from a general-purpose word processor or XML editor to an SPL-specific editing tool. The type of tool suitable for a specific organization will vary depending on a wide variety of business and technical factors. Whatever tool is used, the final SPL document will be independent of the tool used for its creation. All tools should be able to create valid SPL files and to conform to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Content of Labeling*.

20. What is the difference between XML and SPL?

XML is a specification for creating custom markup languages for sharing structured data. SPL is a standard that uses XML.

21. What version of the SPL schema is currently being used by FDA?

The SPL schema currently being used is identified on the FDA Data Standards Council Web site located at www.fda.gov/oc/datacouncil.

22. What happens when a new release of the SPL standard is implemented? Should I resubmit current labels according to the schema in the new release?

We have implemented SPL release 4 to be compatible with the drug registration and listing process. SPL files can be submitted using the schema in SPL release 4 or release 3 until June 1, 2009, when only release 4 can be used.

23. Should I submit patient package inserts (PPIs) and Medication Guides (MGs) in SPL?

Approved patient labeling documents should be included at the end of the SPL file. There are specific Logical Observation Identifiers Names and Codes (LOINC) codes for PPIs and MGs. Use the appropriate LOINC code for identifying this information. Each PPI or MG should have a separate LOINC code.

Patient information that is not approved labeling, such as patient information produced by third parties, should not be included in the SPL file.

24. Should my SPL file contain the entire content of labeling or just the portion of the content that has changed since my last application submission?

All submissions should include the entire content of labeling in SPL. FDA cannot support partial submissions at this time.

25. The SPL standard provides tags to identify insertions and deletions of content in an SPL document. Should I submit a redlined or annotated version of the labeling, indicating version-to-version changes?

No. You should not use the tags provided in the SPL standard to mark up the insertion and deletion of content.

26. Should I include graphics for controlled substance symbols, the Rx symbol or corporate or product logos?

No. These graphics should not be included in an SPL submission. Controlled substance symbols, and other symbols, should be included in the SPL as text (e.g., CII).

27. Can I retain hypertext links within a document if they were present in a Word or PDF file of content of labeling (e.g., clickable cross-references)?

Yes. Hypertext links can be retained within the SPL document. However, these links should correspond only to other portions of the content of labeling, (e.g., see *Dosage and Administration (2)*).

28. Does the FDA distribute SPL documents to the Web with minor changes to the section identifiers submitted?

Yes, at the moment, we correct certain coding omissions and errors. However, when applicants begin using SPL release 4, we will no longer make these corrections.

29. In preparing an SPL, should I update the section identifier when there is a change in a subsection?

Yes.

30. If I relocate a section or subsection without changing its content, should its section identifier be changed?

No. The identifier of a section that is relocated without content change remains unchanged, but the identifiers of any enclosing sections before and/or after the relocation should be changed, as should the document identifier.

31. How is labeling information transmitted to the Web?

Beginning June 1, 2009, FDA will transmit postapproval SPL to the Web electronically from the electronic drug establishment registration and drug listing system, which will then be considered the key repository for postmarket SPL content of labeling. Labeling updates to applications can be made by referencing the SPL file submitted through the drug establishment registration and drug listing process (see question 3 for the Web address).

32. If an applicant identifies a problem with the SPL file posted on the Web site, what should he or she do?

If an applicant notes an inconsistency, he or she should contact the SPL coordinator at spl@fda.hhs.gov and the relevant center's review division to make the necessary changes.

33. When is SPL transmitted to the Web and will FDA notify the applicant when SPL is posted?

No. There is no notification to the applicant that labeling has been posted. Applicants are advised to check the Web site to ensure that their most recently submitted content of labeling is posted.

34. Should an applicant submit SPL with an annual report?

Applicants should submit an SPL file of the content of labeling with an annual report if an SPL file has not previously been submitted for the application, or if there have been changes to the content of labeling since the last submission of final SPL. If there have been no changes since the last submission of final SPL, then the annual report can include a reference to the electronic content of labeling previously submitted.[6]

35. If the first SPL submission is a supplement, should both the current and proposed labeling be submitted in SPL, or is it sufficient to submit the proposed labeling in SPL?

For supplements, only the proposed content of labeling should be submitted in SPL. In addition, annotated labeling should also be submitted for use in the application review process. (See response to Question 5).

36. Where do I find additional information and specifications on SPL?

Additional information is available on the Internet at the FDA Data Standards Council Web site and http://www.hl7.org.

[6] Final SPL is the submission of SPL that is in current use. This includes SPL with approved content of labeling submitted subsequent to the approval of an original BLA/NDA or prior approval supplement; SPL submitted to a CBE supplement (with the initial submission and any subsequent amendments); and SPL submitted to an annual report that contains "annual reportable" changes made since the last submission of final SPL.

37. Should content of labeling in a foreign language be submitted?

Currently, foreign language content of labeling does not need to be submitted in SPL.