Guidance for Industry

SPL Standard for Content of Labeling Technical Qs & As

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

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Electronic Submissions

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I. INTRODUCTION

This guidance is intended to assist sponsors who submit the content of their product labeling to the Center for Drug Evaluation and Research (CDER) using the structured product labeling standard (SPL) in extensible markup language (XML). The guidance also provides information to CDER staff who review and manage that product information using the Electronic Labeling Information Processing System (ELIPS). We anticipate that additional guidance will be provided as new questions arise about the use of SPL and/or ELIPS.

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.

II. 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 the Structured Product Labeling (SPL) Project Development Staff in the Office of Business Process Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), 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 electronically "in a form" that FDA can process, review, and archive. Initially, CDER accepted content of labeling in portable document format (PDF). Then, in anticipation of a change to the SPL format, in September 2004, CDER announced it would accept content of labeling in PDF and in SPL until the fall of 2005 when PDF would be eliminated. On October 21, 2005, CDER announced in public docket number 92S-0251 the following new procedures for electronic submission of content of labeling, effective October 31, 2005:

- PDF is no longer a format FDA can use to accept the content of labeling submitted electronically.
- Sponsors should use the SPL standard when submitting all labels, labeling supplements, and amendments to FDA in XML.

The Agency also announced the development of a new automated system, ELIPS, to process, review, and archive the content of labeling using the SPL standard. This system was also implemented on October 31, 2005.

One of the advantages of using the SPL standard in product labeling submissions is that SPL will make the labeling computer readable. Under a collaboration with the National Library of Medicine (NLM), FDA-approved product information will be sent to the NLM for inclusion in the NLM's DailyMed, an online repository that will make the most current medical product information available to the public on the Internet free of charge.

As a result of initial experience using the SPL format, FDA is providing guidance on a number of technical questions. The Agency plans to provide additional guidance as new questions arise. Please also see the glossary for definitions of useful terms related to the SPL-ELIPS efforts.

- If you have additional questions regarding SPL submissions, you can contact Lonnie Smith at smithlo@cder.fda.gov.

For questions on the guidance for industry *Providing Regulatory Submissions in Electronic Format - Content of Labeling,*[2] contact the appropriate electronic submission coordinator at esub@cder.fda.gov. Specific questions pertaining to content of labeling should be directed to the appropriate review division or office.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

III. TECHNICAL QUESTIONS AND ANSWERS

1. When do I start submitting labeling using the SPL standard?

Beginning October 31, 2005, you should submit the content of labeling to CDER in SPL. This date corresponds with the implementation date for ELIPS. Because ELIPS is compatible with SPL, FDA will use ELIPS to process, review, and archive the electronic content of all labeling for drugs submitted to CDER under an ANDA, NDA, or BLA.

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

SPL is the format for submitting the electronic content of labeling. Electronic content of labeling must be submitted with an original application, with certain amendments and supplements (those that contain changes to the content of labeling), and with annual reports.[3]

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

No. Only the electronic content of labeling is 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, carton labels, and final printed labeling) should not be submitted using the SPL standard.

4. Should a sponsor still submit an annotated Word version of the content of labeling?

Yes. As was previously the case, the annotated labeling should still be submitted. Now, instead of submitting the content of labeling in PDF, as was the previous practice, sponsors should submit it using the SPL standard.

5. Will the sponsor still have to submit the final printed labeling (FPL) (the graphic version of the label)?

Yes. The submission of FPL is still required in § 314.50(e)(2)(ii) of the regulations. The SPL version will only replace the PDF version of the content of labeling.

6. How do I send my SPL to the FDA when I am submitting an electronic submission (i.e., eANDA, eNDA, eBLA, or hybrid submission)?

When submitting the content of labeling using SPL as part of an eANDA, eNDA, eBLA or *hybrid* submission, the SPL version should be included in a folder marked *spl* within the labeling folder (for more information, see the guidance for industry *Providing Regulatory Submissions in Electronic Format - Content of Labeling*).

[3] 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.

7. How do I send my SPL to the FDA when making a paper submission?

When accompanying a paper submission, the SPL version should be sent on electronic media (e.g., a CD or floppy disk). The SPL should be included in a folder marked *spl* (see the 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 where to send SPL.

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

CDER has been accepting SPL, as well as PDF, for the content of labeling since September 2004. At that time, we announced that we would begin to accept only SPL beginning in the fall of 2005. On October 31, 2005, CDER began accepting only SPL for the content of labeling.

10. Will sponsors of generic drugs be granted a grace period (a period of time after the content of labeling for the reference listed drug (RLD) becomes available in SPL), or should they submit SPL beginning October 31, 2005?

We recommend that sponsors contact the Office of Generic Drugs for questions about timing of submissions of generic drug SPL.

11. For generic drug SPL submissions, should we include the content of the labeling for the RLD electronically?

The content of labeling for the RLD may be provided in paper or electronic format.

12. 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?

A combination of paper submission and electronic labeling can be submitted.

13. Does the SPL content of labeling replace the 12 copies of paper labeling normally submitted, or is it in addition to the 12 paper copies?

The content of labeling (which was in PDF, but is now in SPL format) is in addition to the 12 copies of paper labeling (see 314.50(L)(1)(i)).

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

No. SPL should be submitted to the Agency's Electronic Document Room with documentation appropriate for the type of electronic submission.

15. Should we submit MS Word and/or PDF with the SPL?

You should no longer submit the content of labeling in PDF. However, sponsors can submit PDF versions of other labeling (e.g., cartons, container labels, paper inserts).
If labeling discussions are occurring in MS Word (expected initially), at this time, FDA requests that sponsors provide the MS Word file to support review of the labeling.

16. If we do not have the technology to submit the labeling in eCTD format, can we submit it in electronic NDA format?

Yes. You can submit in eNDA format.

17. Where should SPL be submitted if it contains both paper and electronic components?

Both components should be sent to the central document room (as was done before implementation of SPL). As before, the staff will upload the electronic component.

18. Should the sponsor submit SPL to FDA before labeling discussions are complete?

Yes. SPL should be included with the initial submission. Before an approval action, FDA may ask a sponsor to submit SPL updated to include the changes that occurred as a result of labeling discussions with the Agency.

19. Should companies resubmit labels submitted before October 31, 2005, in SPL that are currently under review?

No, but sponsors should work with the individual review division or divisions to ensure that SPL is available for new products within a reasonable time frame.

20. Is it possible that the FDA will refuse to file my submission if I do not provide SPL beginning October 31, 2005?

That is a possibility, but we will work with you to help you submit the SPL.

21. What software do I use to create SPL?

An SPL document can be created using a variety of possible 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 upon a wide variety of business and technical factors. Whatever tool is used, the final SPL document will be independent of the tool used for creation; all tools should be valid against the SPL schema and should conform to FDA guidance documents.

22. What is the difference between XML and SPL?

XML is a standard language for exchanging structured information or documents. The details are frequently provided in what is called a schema. SPL is a standard for exchanging the information in product labeling using XML. The details for the SPL XML submission is in a schema.

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

The SPL schema currently being used is on the FDA Web site at http://www.fda.gov/oc/datacouncil/spl.html. This version is a subset of the full HL7 SPL Release 2 schema.

24. What happens when a new version of the schema is released? Should sponsors resubmit current labels according to the new schema?

When the SPL schema is revised, FDA will inform sponsors regarding the time frame for implementation. We anticipate that resubmissions will not be necessary if a new schema is adopted. However, this policy depends on the specific schema changes adopted.

25. Should I submit patient package inserts (PPIs), medication guides (MedGuides), and patient information leaflets (PILs) in SPL?

If your package insert has a PPI, MedGuide, or PIL at the end, that information should be included in SPL. There is a specific LOINC code for *Supplemental Patient Information* (i.e., patient information following the ***How Supplied*** section of labeling) and for the PPI and the MedGuide subsections of the ***Supplemental Patient Information*** section. Each of the approved patient labeling documents should have a separate LOINC code.

Patient information that is not part of the approved labeling, such as patient information produced by third parties, should not be included in SPL. Questions regarding the inclusion of approved labeling for patients in SPL should be directed to ONDEIO@cder.fda.gov or to the appropriate review division.

26. Should SPL contain the entire content of labeling or just the portion of the content that has changed since the last submission?

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

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

No. You should not use the tags provided in the schema to mark up the insertion and deletion of content. Using SPL instead of PDF will not affect the labeling discussions with FDA (including the submission of redlined and annotated documents).

28. Should manufacturer-specific graphics (e.g., registered trademark symbols, controlled substance symbols, corporate or product logos) be used in SPL?

No. Corporate or product logos, or similar graphics, are not considered part of the content of labeling and therefore should not be included in SPL. Trademark symbols can be included using standard text and *unicode characters*. Controlled substance symbols can be provided as text (e.g., CII)

29. Should a graphic for the Rx symbol be used in SPL?

No. The document LOINC code for SPL will identify SPL as human prescription drug labeling.

30. Can a sponsor retain within-document hypertext links 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 be restricted to *semantic* links that are strictly identified within the content of labeling (e.g., "*see* CLINICAL PHARMACOLOGY," or "*see* references/footnotes"). Because links to documents outside of the SPL document may change without a change in the content of labeling, they should not be used.

31. Can there be more than one title in a header (e.g., *Example Tablets, 10 mg,* and *Example Suspension, 1 mg/mL*)?

No. There should only be one <title> element in SPL. However, the schema permits
 tags within the <title> element for multiline titles.

32. Will the FDA distribute SPL documents to the NLM with minor changes to the sections without changing the section identifiers from those submitted?

No. FDA will change the section identifiers from those submitted when it transmits the SPL to the National Library of Medicine (NLM), consistent with the principle that new identifiers should be changed when a section (or an enclosed section) changes.

33. Does the scope of a section identifier include its subsections?

Yes. The scope of a section identifier is all of the child elements of that section.

34. If a section or subsection is relocated without change to 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.

35. Can SPL have a section that contains other sections but does not contain any other text?

Yes. A section can contain only subsections and no text. For example,

Precautions

General: The use of this drug may promote . . .
Skeletal Muscle: In Phase 3 complicated skin and skin structure infections . . .

36. Are the active and inactive ingredients included in the data elements?

Yes. All the active ingredients and inactive ingredients in the content of labeling are included as data elements.

37. How is labeling information transmitted to NLM?

FDA electronically transmits SPL to NLM.

38. How will the sponsor know that the correct (i.e., agreed upon) labeling is transmitted to NLM?

The sponsor will receive a rendering of the content of labeling transmitted to NLM with the action letter.

39. If the sponsor notes an inconsistency in the label, what is the process to make the necessary changes?

As was previously the case, if a sponsor notes an inconsistency, the sponsor should contact the review division.

40. Will FDA notify the sponsor when SPL is posted?

No. SPL is processed using ELIPS with defined procedures for allowing sponsors to know when to expect the posting of labeling changes. There is no specific notification to the sponsor that a label has been posted to NLM.

41. Should I submit SPL with an annual report? And should two paper copies of an NDA annual report still be submitted to the appropriate review division?

Submit SPL with your annual report if this is your first SPL submission since October 31, 2005, or if there have been changes to the content of labeling since your last SPL submission. If there have been no changes since your last submission of SPL, then it is not necessary to submit any SPL with an annual report. Two paper copies of formatted labeling with each annual report are still required under 21 CFR parts 314 and 601.

42. What is the process for the review of SPL content of labeling submitted with an annual report? When is the SPL transmitted to NLM? How will the sponsor be notified?

For annual reports that contain the first submission of SPL for a specific application, FDA will forward the SPL to NLM after review of the content of labeling. Because annual reports contain the version of labeling in current use, the sponsor will not be notified unless the FDA reviewer finds a problem that should be corrected.

43. If the first SPL submission is a supplement (i.e., not an annual report), should both the current and proposed labeling be submitted in SPL, or is it sufficient to submit only the proposed label in SPL?

For supplements, only the proposed content of labeling should be submitted in SPL.

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

See *FDA Data Standards Council Structured Product Labeling Resources* on the Internet at http://www.fda.gov/oc/datacouncil/spl.html and http://www.hl7.org

45. Should the Spanish language directions for use be submitted?

Currently, foreign language directions do not need to be submitted in SPL.