Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Content of Labeling

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Providing Regulatory Submissions in Electronic Format — Content of Labeling

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

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Guidance for Industry[1]

Providing Regulatory Submissions in Electronic Format — Content of Labeling

> This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This is one in a series of guidance documents intended to assist applicants making regulatory submissions to FDA in electronic format. Agency guidance documents on electronic submissions will be updated regularly to reflect the evolving nature of the technology and the experience of those using this technology.

The Agency is adopting new technology for processing and managing labeling and labeling changes, including the content of labeling submitted electronically. This guidance describes how to submit the content of labeling using the Structured Product Labeling (SPL) standard, which is based on extensible markup language (XML).

This guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biologic products, including new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biological license applications (BLAs) for biological products that meet the definition of drug in the Federal Food, Drug, and Cosmetic Act. The *content of labeling* is the labeling required under 21 CFR 201.100(d)(3) including all text, tables, and figures (commonly referred to as the package insert or professional labeling). This guidance applies to the content of labeling provided with original submissions, supplements, and annual reports. Copies of the formatted label and labeling and

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[1] This guidance has been prepared by the Information Management Program in the Center for Drug Evaluation and Research (CDER).

specimens of enclosures required elsewhere in the regulations (e.g., 21 CFR 314.50(e)(2)(ii)), including carton and container labels, must still be submitted either electronically in Portable Document Format (PDF) or on paper.

For a list of guidances that are under development on electronic submissions, see the guidance *Regulatory Submissions in Electronic Format — General Considerations.*[2] The general considerations guidance also addresses issues (e.g., appropriate file formats, media, and submission procedures) that are common to all submission types.

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

A.   The Electronic Labeling Rule

On December 11, 2003, FDA published final regulations (the electronic labeling rule) requiring the submission of the content of labeling in electronic format for marketing applications (68 FR 69009). The requirements of the electronic labeling rule can be found in § 314.50(l) for NDAs, § 314.94(d) for ANDAs, § 601.14(b) for BLAs, and § 314.81(b) for annual reports to marketing applications. The effective date of the rule was June 8, 2004. The regulations specify that the content of labeling must be submitted electronically in a form that FDA can process, review, and archive. The regulations also state that FDA will periodically issue guidance on how to provide the electronic submission. This guidance provides information on how to submit the content of labeling in electronic format.

B.   New Technology for Processing Labeling
     and Labeling Changes

The regulations require that the content of labeling be submitted in a form that we (FDA) can process, review, and archive. Since 1999, FDA has been receiving the electronic content of labeling in Portable Document Format (PDF), and this format has allowed us to process, review and archive the content of labeling. Recently, however, recommendations from the Institute of Medicine and the National Committee on Vital and Health Statistics and mandates in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173) have created a new role for electronic labeling information. Electronically formatted content of labeling will be used to support health information management technologies such as electronic prescribing; the electronic health record (EHR), which will provide health care

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[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 and the CBER guidance page at http://www.fda.gov/cber/guidelines.htm.

providers, patients, and other authorized users access to patient information in electronic format; and the DailyMed, a new way to distribute up-to-date and comprehensive medication information in a computerized format for use in health care information systems.

We have determined that our current procedures using PDF are not adequate to support these electronic initiatives. To support the new programs, the Agency is changing the way it processes, reviews, and archives the content of labeling. The Agency is adopting a new technology for exchanging information between computer systems based on Clinical Document Architecture (CDA). CDA was developed by Health Level Seven (HL7), a standards development organization accredited by the American National Standards Institute (ANSI). CDA allows information to be exchanged in extensible markup language (XML) and is the standard being investigated for the EHR.

FDA, working with other parties in HL7 (experts from HL7, industry, and technology solution providers), has adapted CDA for labeling in an HL7 standard called Structured Product Labeling (SPL). When compared with PDF, SPL exhibits the following advantages.

- SPL allows the exchange of information between computer systems in a way that cannot be accomplished with PDF. For example, the information in SPL can be used to support health information technology initiatives for improving patient care.
- The exchange of labeling changes with SPL can be easier and more efficient for both FDA and manufacturers when compared with PDF. For example, with SPL, only those sections or data elements of the labeling that are changed would need to be checked rather than the entire labeling.
- SPL allows automation of comparison of text by section and comparison of specific drug information data elements.
- SPL can also be used to exchange information needed for other submissions, such as drug listing, thus eliminating redundant data collection and improving efficiency.

The Agency is developing an automated system using SPL for processing and managing labeling and labeling changes. The Center for Drug Evaluation and Research has identified SPL in public docket number 92S-0251 as a format that FDA can use to process, review, and archive the content of labeling. During our transition to the automated system, the Agency is able to accept the content of labeling in either PDF or SPL file format. After the automated system is implemented, PDF will no longer be a format that we can use to process, review, and archive the content of labeling. The change to SPL will apply only to those submissions with content of labeling files that are provided after the implementation of the automated system. At this time, it is our goal to complete the transition to SPL format for content of labeling submissions for approved prescription drugs by fall 2005.

The Agency is changing to SPL format so the content of labeling can be used in a variety of ways — searched, moved between systems, combined with other data sources — to support electronic health initiatives. At this time, the Agency will continue to receive other parts of electronic applications in the formats described in applicable Agency guidance on electronic submissions.

III. GENERAL ISSUES

This guidance applies to the content of labeling for any marketing application (ANDAs, BLAs, NDAs) submission required to be submitted in electronic format under §§ 314.50(l) 314.81(b)(2), 314.94(d), and 601.14(b).

A. File Formats for Providing Content of Labeling

Prior to the implementation of the automated system, we will be able to receive content of labeling in PDF or SPL file format. After implementation of the automated system, we will only be able to receive content of labeling in SPL format.

This guidance describes how to submit the content of labeling using XML based on the HL7 SPL specifications.

For information on how to submit the content of labeling using PDF based on the Adobe Systems Incorporated specifications, see the current Agency guidance on providing regulatory submissions in electronic format.[3]

B. Creating the Content of Labeling File

Please refer to the HL7 published specifications for Structured Product Labeling (SPL) for details on how to create the content of labeling file for submission to FDA. The SPL specifications can be obtained from HL7 (www.hl7.org). Additional details on creating SPL for submission to FDA can be found in the HL7 document *SPL Implementation Guide for FDA Content of Labeling Submissions*. The implementation guide may be found on the HL7 web site at http://www.hl7.org. Links to SPL-related documents located on the HL7 Web site and additional SPL-related resources (including the most recent updates, stylesheet files for viewing SPL files, and example labels) can be found at the FDA Web site at www.fda.gov/oc/datacouncil/spl.html.

Bookmarks commonly included in the PDF content of labeling files to sections within the labeling are not needed because the tags in the SPL file provide this functionality. SPL does not replace various methods used for negotiating labeling changes (e.g., FAX, Word files). Prior to the implementation of the automated system, FDA can accept content of labeling submitted in SPL file format only in a complete SPL file. Submission of multiple versions of the labeling (e.g., "proposed" or "current") and submission of the *history.pdf* file can be eliminated only after the implementation of the automated system.

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[3] See the guidances for industry entitled *Providing Regulatory Submissions in Electronic Format — NDAs* and *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. 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 or the CBER guidance page at http://www.fda.gov/cber/guidelines.htm.

C.   Procedures for Sending the Content of Labeling

Content of labeling must be provided in electronic format (§§ 314.50(l), 314.94(d), 601.14(b), and 314.81(b)), even when it is part of a paper submission. Before implementation of the automated system, you should follow the procedures in either this guidance or Agency guidance on submitting electronic NDAs or BLAs[4] for information on how to submit the content of labeling electronically. After implementation of the automated system, you should follow the procedures in this guidance for submission of the content of labeling electronically.

Note: In order for FDA to process, review, and archive electronic content of labeling, all submissions, including annual reports, must be made in accordance with certain provisions of 21 CFR part 11 specified in the electronic labeling rule (§§ 314.50(l), 314.94(d)(1), 601.14(b), and 314.81(b)) and sent to the appropriate central document room facilities specified in public docket number 92S-0251. Electronic documents that are sent directly to division document rooms or to reviewers bypass the controls established for the receipt and archiving of documents and, therefore, are not considered official documents for review.

D.   Technical Problems or Questions

If you have any questions on technical issues related to providing the content of labeling in submissions according to the recommendations in this guidance, please contact the appropriate electronic submission coordinator at esub@cder.fda.gov or esubprep@cber.fda.gov. Specific questions pertaining to content should be directed to the appropriate review division or office.

IV.   ORGANIZING THE MAIN SUBMISSION FOLDER

The content of labeling SPL files should be placed in a single folder titled *spl*. The spl folder is used for all submissions in SPL whether they are part of an electronic submission or a paper submission.

If the content of labeling in SPL is provided with an electronic submission, you should place the *spl* folder in the appropriate folders for labeling. For additional information on organizing the submission folder in an electronic submission, see current Agency guidance on providing regulatory submissions in electronic format.[5]

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[4] For content of labeling submitted as part of a paper submission, see the guidances for industry entitled *Providing Regulatory Submissions in Electronic Format — NDAs* and *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*.

[5] See footnote 3.