Guidance for Industry

Indexing
Structured Product 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)

June 2008
Electronic Submissions

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I. INTRODUCTION

This guidance explains that FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will index the content of labeling for human drug and biological products using SPL (Structured Product Labeling). Indexing refers to the insertion of machine-readable tags, which do not appear in actual printed labeling, that enable users with clinical decision support tools and electronic prescribing systems to rapidly search and sort product information. This guidance also describes how applicants can participate in the SPL indexing process. Having consistently and accurately indexed content of labeling is an important step toward the creation of a fully automated health information exchange system.

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. When Did the Use of SPL Become a Requirement?

On October 31, 2005, FDA stated that SPL in extensible markup language (XML) format is the only electronic format for content of labeling[2] that CDER can process, review, and archive.[3]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] Content of labeling refers to all text, tables, and figures associated with prescribing information. It does not include carton and immediate container labels.

This also applied to annual report submissions.[4] Currently, the content of labeling must be submitted to CBER in electronic format (21 CFR § 601.14; see also guidance for industry: *Providing Regulatory Submissions in Electronic Format-Content of Labeling*). CBER soon will begin recommending that content of labeling be submitted in SPL. SPL is also a key component of Facts@FDA,[5] which makes regulated product information in SPL format publicly available on the National Library of Medicine's DailyMed Web site and on the FDA Data Standards Council Web site ("Data Standards Web site").[6]

A Health Level Seven (HL7)[7] standard, SPL is used to make possible the electronic exchange of the content of labeling and other regulated product information using the extensible markup language (XML). Specifically, the SPL standard enables the inclusion of *indexing elements*, which are machine-readable tags that can be added to product labeling to enable users to rapidly search and sort product information.

B. Why Is Indexing SPL So Important?

Indexing the content of labeling with SPL will greatly enhance users' ability to automatically search and sort product information. The American healthcare community (*e.g.*, federal healthcare agencies, healthcare providers, healthcare professionals, and industry) is working toward the creation of a fully-automated health information system. Eventually, patients, healthcare professionals, and providers will have electronic health records, electronic prescribing systems, and an array of clinical decision support systems and tools at their disposal. Being able to electronically access labeling information and to search and sort that information is an important step toward the creation of a fully automated health information exchange system.

Currently, health information suppliers take the information from the content of product labeling to populate databases that are used in clinics and hospitals to help prevent prescribing errors. In the past, much of this information was input by hand. Since October 31, 2005, FDA has been making labeling information for prescription drugs available free of charge on the Internet through the use of SPL. Full-text search of the content of labeling has obvious limitations, however. For example, users searching for *hepatotoxicity* will miss labelings that use the term

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[3] See 21 CFR §§ 314.50(l)(1)(i) and (l)(5) and 314.71(b); see also Memorandum 32 ("Content Labeling") to FDA Docket No. 92S-0251.

[4] *See* Guidance for Industry: *SPL Standard for Content of Labeling Technical Qs & As*, Question #41. See 21 CFR 314.81(b)(2)(iii) (note, however, that applicants should not submit SPL with an annual report if there are no changes to the previously submitted SPL).

[5] *See* http://www.fda.gov/oc/datacouncil/drug_labels.htm.

[6] *See* http://dailymed.nlm.nih.gov/dailymed/about.cfm and http://www.fda.gov/oc/datacouncil/drug_labels.htm.

[7] *See* http://www.hl7.org. HL7 is a one of several American National Standards Institute-accredited Standards Developing Organizations (SDOs) operating in the healthcare arena. Most SDOs produce standards (sometimes called specifications or protocols) for a particular healthcare domain such as pharmacy, medical devices, imaging or insurance (claims processing) transactions. Health Level Seven's domain is clinical and administrative data.

liver toxicity. The addition of indexing elements, chosen from standards adopted for use in the healthcare setting, will address this problem.

Once FDA has indexed the content of labeling using SPL, health information suppliers will be able to package indexed information about a product and make it available to healthcare professionals and others through health information systems, such as clinical decision support tools and electronic prescribing systems. In addition, the prescription drug information that FDA already has made available on the Internet will be much more useful, because the indexing elements will enhance user ability to quickly access, search, and analyze the labeling information needed to make critical healthcare decisions. SPL indexing elements are not intended to be used by clinicians in lieu of the full prescribing information, nor do they serve as the basis for product promotional activities.

Having consistently and accurately indexed content of labeling also will greatly enhance the safe use of medical products. In July 2006, the Institute of Medicine of the National Academy of Sciences estimated that more than 1.5 million people annually are injured due to medication errors. The cost of treating hospital-based medication errors alone is conservatively estimated at more than $3.5 billion annually, and this cost does not include estimates for lost wages and lost productivity.[8] One source of many errors is prescribing errors, which can result in avoidable adverse drug reactions. For instance, if a patient with asthma is taken to the hospital in an emergency situation for an unrelated physical injury, the SPL indexing elements would enable the hospital to use its computer system to quickly identify all drugs contraindicated in patients with asthma and treat the patient accordingly. Among other benefits, the SPL indexing elements also could enable the hospital's computer system to ensure that medications prescribed by the hospital to treat the patient's injury do not adversely interact with other medications that the patient is taking to treat his or her asthma. In short, the SPL indexing elements, when coupled with other computer technologies, will provide patients and healthcare providers with better and ***more timely*** access to important healthcare information.

Finally, indexing the content of labeling directly supports FDA's mission, because this effort will help Americans "get the accurate, science-based information they need to use medicines … to improve their health."[9] Indexing also addresses a recommendation in the Institute of Medicine's 2006 report on drug safety, which identified the need for improved communication between FDA and the public about drug safety and efficacy information.[10] SPL indexing will greatly facilitate this communication by helping create a more robust nationwide system for promoting the safe and effective use of drugs.

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[8] *See* http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11623.

[9] *See* FDA Mission Statement at http://www.fda.gov/opacom/morechoices/mission.html.

[10] *See* "The Future of Drug Safety: Promoting and Protecting the Health of the Public," cited at http://www.iom.edu/CMS/3793/26341/37329.aspx.

III. FDA'S STRATEGY FOR INDEXING SPL

A. Why Is FDA Indexing SPL?

FDA has been piloting the addition of SPL indexing elements to labeling that has been submitted by sponsors pursuant to the new content and format regulation for prescription drug labeling.[11] Although a number of different approaches were tried during the pilot program, based on our experience and on feedback from industry and other SPL users, we have determined that the most efficient strategy is for FDA, rather than individual applicants, to index the information received in SPL. Moreover, it is important that indexing be done consistently to enable comprehensive searches to find all relevant information, including appropriate synonyms. FDA's exclusive indexing of the SPL information furthers this goal.

B. How Will FDA Index SPL?

FDA will index the content of labeling for all products. The process therefore is not limited to products subject to 21 CFR 201.57 during the implementation period for that regulation.

FDA intends to index the content of labeling using a phased implementation. Phased implementation will help maximize the utility of the indexing elements given available Agency resources and will ensure that all labeling will contain key indexing elements during the initial phases of the SPL indexing process. For drug and biological products, indexing information includes, among other things, the indication, limitations of use, conditions of use, and pharmacologic class of the drug. In the first phase, FDA plans to index the pharmacologic class for all labeling in SPL. We are indexing pharmacologic class first because (1) it is important for the safe use of drugs, (2) it is necessary for making future indexing meaningful (e.g., drug interactions), and (3) this choice leverages existing FDA resources. After pharmacologic class, FDA will decide which indexing elements should be added in future phases, and those decisions will be posted on the Data Standards Web site. FDA will solicit public input from SPL users and industry through public meetings and announcements (e.g., in the *Federal Register*) prior to announcing new indexing elements.

```
<generalizedPharmaceuticalClass>
    <code code="N0000000184" codeSystem="2.16.840.1.113883.3.26.1.5" displayName="monoamine
oxidase inhibitors"/>
</generalizedPharmaceuticalClass>
```

[11] *See* Guidance for Industry: *SPL Standard for Content of Labeling Technical Qs & As*.

FDA generally will make indexing decisions based on the content of labeling and the selected terminologies.[12] For example, the pharmacologic class indexing element for a monoamine oxidase inhibitor is associated with the preferred term "monoamine oxidase inhibitors" and the associated code (N0000000184) from the Veterans Administration National Drug File Reference Terminology (NDF-RT).[13] FDA would index a monoamine oxidase inhibitor as follows:

Because indexing serves only to electronically flag or identify information of a particular type, indexed elements are not visible in the printed labeling. These tags nonetheless can be used to sort and categorize the information so that it will be more readily accessible in electronic systems.

FDA will use a coordinated approach for indexing to ensure consistency across all labeling and will consult with subject matter experts in the respective Centers' review divisions as necessary. To make the process as transparent as possible, FDA intends to list on the Data Standards Web site the terminologies and elements it plans to use to index the SPL for all labeling.[14] To that end, FDA first will post for comment a list of pharmacologic class terms that it has selected for FDA-regulated active ingredients prior to indexing SPL containing those ingredients. Instructions on providing comments to these listings will be included on the Data Standards Web site. FDA intends to periodically update the term list. FDA may employ a similar announcement strategy for future indexing elements.

C. Participation in SPL Indexing

Applicants may suggest indexing terms when they submit their SPL file in their regulatory submission. See the SPL Implementation Guide for details on including indexing terms.[15] Because FDA will be indexing the content of labeling, applicants should not change indexing elements associated with existing SPL.

In general, the SPL indexing process is independent from the labeling review process associated with a submission review cycle. As such, SPL indexing will not affect review times or delay approvals. However, indexing considerations may be incorporated in the standard labeling review discussions. Because FDA will add indexing terms as a separate file that references the SPL, the applicant's SPL file will remain unchanged by the indexing process.

We recommend that applicants submit any questions regarding an existing indexing element, including any requests to add or revise an element, to spl@fda.hhs.gov. Inquiries and requests

[12] If an appropriate term is not available in an existing terminology, FDA will work with the relevant terminology maintenance organizations to identify a new term.

[13] NDF-RT includes the controlled terminology for mechanism of action, physiologic effect, and structural class, which are part of the Federal Medication Terminology standard.

[14] The timing of subsequent phases will depend on available FDA resources.

[15] The Implementation Guide can be found on the HL7 Web site at http://www.hl7.org or the Data Standards Web site at http://www.fda.gov/oc/datacouncil/spl.html.

will be forwarded to the appropriate FDA personnel, who will consider them and make any appropriate change to the indexing element.

Disagreements that cannot be resolved at this level should be handled according to procedures outlined in the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*.