

Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs



5710 April 2, 2004

Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0041; Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Content of Labeling; 69 Federal Register 5552; February 5, 2004

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over \$32 billion in the discovery and development of new medicines.

General Comments

PhRMA supports the concept of providing the content of labeling for marketing applications in electronic format – a form that FDA can process, review and archive. We appreciate the information provided in the draft guidance on submitting the content of labeling in electronic format. Our comments and questions fall into two areas – the feasibility of implementing the Structured Product Labeling (SPL) standard in the suggested timeframe and some specific operational topics.

Implementation of the Structured Product Labeling Standard

PhRMA supports the development of the Structured Product Labeling (SPL) standard, provided that adequate time is devoted to properly developing and thoroughly testing its use by industry and the FDA. The implied requirement for providing electronic labeling in the SPL format by the end of 2004 is unrealistic, because of a variety of factors, including lack of clarity around the SPL specification (which is very complex), lack of adequate vendor support (at this time), and unclear requirements and capability for converting legacy labeling documents (in WORD and PDF format) to XML-based documents in the SPL format.

A critical implementation issue is that industry does not have clear guidance on the development of a valid SPL-compliant label. The PhRMA Electronic Regulatory Submissions Working Group has formed a dedicated task group to study the SPL specification, and to develop a style sheet for presentation of an SPL-compliant package insert, to develop a

2004D-0041

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Pharmaceutical Research and Manufacturers of America

practical implementation guide for the pharmaceutical industry and to help test this with the FDA later this year. The knowledge gained from this task group initiative will help industry understand the SPL specification and implement it within a reasonable timeframe. Additionally, PhRMA believes that there will be benefit from understanding further FDA's Electronic Labeling Information Processing System (ELIPS) system and how this system will handle SPL documents prior to widespread implementation of the standard. Therefore, PhRMA requests that FDA not impose the SPL requirement at the end of 2004, but, instead, provide more time for FDA, PhRMA, vendors and HL7-affiliated groups to partner together to prepare for, test and implement the SPL specification.

One PhRMA member company has been working for the past 18 months to understand the labeling processes and develop an appropriate XML-based IT system to support those processes. Despite their work in this area, it is unlikely that even they will be able to comply with the year-end deadline, given the incomplete understanding of implementation requirements and the complexity and expense associated with document conversion to the SPL standard.

At a minimum, it is estimated that it will take approximately six to nine months from the time of availability of a commercially available system for a company to set up, configure, validate and test a system. This would require sponsor resources (including system purchase, resources for business process changes, training, etc.) that have not been budgeted for 2004 and that will need to be considered in future business-planning cycles. PhRMA is aware of one vendor who has developed an XML-based system, but the capability of this system to enable conversion to a WORD document is unclear. This could have significant implications, as other aspects of the business require the use of a WORD document, requiring a sponsor to use an alternative method to create and possibly store these documents - a solution that imposes a significant burden.

The PIM (Product Information Management) project in Europe has many similarities to the SPL specification. The PIM project, despite widespread industry and agency support over the past few years, has encountered numerous challenges with the details of the PIM specification that only recently came to full light after some extensive testing with real data. PhRMA believes that an extensive testing period is needed before industry and FDA can reasonably adopt a position on the SPL specification. We suggest a pilot test, co-sponsored by FDA and industry, to enable trial use of the SPL specification.

The shift to SPL will require a systemic change if the true value of XML is to be appreciated. If all that is accomplished is a transformation of a WORD document to XML at the end of the process, then this will simply be an added burden for industry. Sponsors will need time to assess the impact that this systemic change will have on authoring and submission processes, their authors and publishers, their support organizations, trainers, and the exchange of information with reviewers at the FDA.

Another significant issue is the conversion of existing labeling documents to XML. The majority of labeling department personnel in the industry are not currently equipped with the knowledge to craft an SPL-compliant label. Internally or externally developed technology solutions must be created, tested, validated, and implemented, and employees must be trained on their use. Again this will require time and resources not currently budgeted. Therefore, complete

implementation of the SPL before the end of 2005 is not feasible for PhRMA member companies.

Specific Comments

I. INTRODUCTION

The "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format," published in December 2003, defines the "content of labeling" as "the contents of the package insert of professional labeling, including all text, tables, and figures for prescription products." PhRMA wants to clarify that the new guidance would require company to submit the SPL file only for the content of labeling; for example, a company currently submits the annotated version of the labeling and cartons and container labels as PDF. If these documents are included in a submission, would companies need to submit them in SPL, or can they continue to submit them as PDF?

II. B. New Technology for Processing Labeling and Labeling Changes

Lines 100-104 of the draft guidance state, "During our transition to the automated system, the Agency would be able to accept the content of labeling in either PDF or SPL file format. After the automated system is implemented, PDF would no longer be a format that we can use to process, review, and archive the content of labeling. At this time, it is our goal to complete the transition to SPL format for content of labeling submission by the end of 2004." PhRMA requests additional guidance to address the following questions:

- Would labeling documents (for new products and changes to existing labeling) already submitted to the agency during this transition period need to be re-submitted to the agency in SPL format, or would they be exempted?
- If companies would not be required to re-submit, then would they also be allowed to continue submitting labeling documents in WORD and/or PDF during any subsequent label negotiations with the agency, or would we be required to submit changes during label negotiations in SPL format?

III. GENERAL ISSUES

Lines 109-111 of the draft guidance state, the regulations regarding Annual Reports are not mentioned. However, lines 32 and 55 indicate the guidance applies to Annual Reports. Please clarify.

III. B. Creating the Content of Labeling File

Lines 126-127 of the draft guidance state, "The SPL specifications are available on the Internet at http://hl7.org/lib_admin/docs.cfm?dir=library\committees\clinicaltrials&comm=rcriim."

- There is no style sheet defined for the presentation of labeling in the specification. We believe the specification is not complete without a standard definition for a human readable format.
- Please consider including a simplified version of the HL7 published specifications in the guidance. The link takes you to a very large document with specifications that are very technical in nature and difficult to understand. An example of a marked-up package insert in the guidance would provide industry a visualization of what the final document should look like after the specifications are implemented.

Lines 127-129 of the draft guidance state, "For submission of labeling changes, you should only submit the labeling section or data elements that have changed."

- If multiple sections of a labeling document change, will each section of the label be a separate file?
- If a change involves adding a cross-reference to a section of the labeling, should a company also submit the section that is being referred to, even if no changes have been made to that section? For example, if a company adds "See CONTRAINDICATIONS" to the PRECAUTIONS section of a labeling document, should they submit the CONTRAINDICATIONS section in an SPL file, even if that section has not changed?
- How should a company identify what has changed in the SPL file? Should changes be shown using some type of revision marks, or does the agency want to receive a clean SPL file to compare against a previous version of the content of labeling? The SPL specification includes "Delete" and "Insert" capabilities, which can be used to designate the changes in an SPL file. Please provide guidance on the preferred way to submit revised text to the FDA in an SPL file.
- When submitting the labeling in SPL format, will both a clean text SPL document and a marked text document be required as is currently?
- Will the label be a single file with the ability to update/submit sections?
 - If so, how will life cycle work (especially if a sponsor submits a new file with multiple, but not all, sections)?
 - As the label is modified, will the label be a single file that will grow to maintain all of the history within it?
- Will it become necessary for ALL submissions to contain the most current labeling (assuming the complete label will consist of the original plus all amended sections)?

III. C. Sending the Submissions

Lines 136-140 of the draft guidance state, "All submissions must be sent to the appropriate central document room facilities as required under 21 CFR part 11. Electronic documents that are sent directly to the review division document rooms or to reviewers bypass the controls established for the receipt and archiving of documents and, therefore, are not considered valid documents for review." The Annual Report currently is submitted to the FDA division responsible for reviewing the application (21CFR314.81(b)(2.)) This draft guidance, however, states that as an electronic submission, the content of labeling should go to the Central Document Room. When submitting an Annual Report, should a company send the content of labeling SPL file to the Central Document Room and send the Annual Report to the review division, or will the regulations be changed so that the Annual Report will now be sent together with the SPL file to the Central Document Room?

IV. ORGANIZING THE MAIN SUBMISSION FOLDER

Line 152 of the draft guidance states, "The content of labeling SPL file should be placed in a single folder titled *SPL*." PhRMA would like to clarify that the folder titled "SPL" is only needed when a company is providing the content of labeling SPL file with a *paper* submission. In other words, when an electronic submission is prepared, the additional "SPL" folder does not need to be included. Instead, would the company include the SPL file in the Item 2 labeling folder, as described in "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"?

Line 154 states, "If the content of labeling in SPL is provided with an electronic submission, you should place the file in the appropriate folders." For electronic submissions, PhRMA requests clarity around the following questions:

- Does the SPL file replace or change any or all of the following documents currently included in an electronic submission: "proposed.doc," "proposed.pdf," "proposed_clean.doc," "proposed_clean.pdf?" Or does a company include the SPL file in addition to these four documents?
- If the SPL file is included in addition to the four documents indicated above
 - What should we name this file in the labeltoc? Would "content of labeling" appear in labeltoc?
 - Does the SPL file belong within the main folder (e.g., top level) or within the labeling folder?
- Current guidances for submission in electronic format require that labeling documents include bookmarks. How are bookmarks provided in the SPL?
- Please clarify the following cases:
 - In an electronic submission, should a company submit the supporting DTD/schema and style sheet? If so, where should these files be located?
 - In an eCTD submission, please clarify on which of the nodes under m1-14 the SPL file format could/should be submitted.
 - In an eCTD submission, how does the use of SPL impact the use of history.pdf and its contents?
 - In an eCTD submission, please clarify if the SPL folder is still expected to be used and confirm that this folder would reside under the "us" folder.
 - In an eCTD submission, if multiple SPL formatted files are to be submitted (e.g., to meet the needs of the various subsections of m1-14), please indicate whether all SPL files should be included in a single SPL folder or multiple SPL folders should be used; and also clarify whether a specific file nomenclature is required.
- Assuming that any graphic or image files included in labeling would be referenced by the SPL and not included within the SPL, please confirm the location of these files (e.g., in an SPL folder or a sub-folder under the SPL) and any required file formats (e.g., mol files or CML for chemical structures) or file nomenclature associated with these files.
- More direction must be provided on the requirements for labeling submissions using SPL and created in XML. Consideration should also be given to provide an additional guidance or updating the January, 1999 Guidance, Regulatory Submissions in Electronic Format, New Drug Applications, to provide direction as to the information and structure of labeling submissions, and descriptions and naming conventions for the individual data elements.

Other Comments:

- Regarding the use of codes managed by LOINC (Logical Observation Identifiers Names and Codes), who will have the responsibility to direct the management of this code list by LOINC (e.g., FDA, RCRIM or another group)?
- Both eCTD (using the operation and modified file attributes) and CDA/SPL (using document id, versionNumber, RelatedDocument and relatedDocument.typeCode) have the ability to manage lifecycle relationships between files. Additionally, CDA/SPL has the ability to manage relationships between sections across different files. Please

explain how the lifecycle capabilities within eCTD and CDA/SPL will work together and which will take precedence if they appear to disagree.

- Will the EVS validate the SPL file(s) upon check-in of the submission?

PhRMA appreciates the opportunity to submit these comments and looks forward to continuing to work collaboratively with the agency on this important initiative.

Sincerely,

A handwritten signature in black ink, appearing to read "Alan Goldstein". The signature is fluid and cursive, with a long horizontal flourish extending to the right.