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July 29, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher's Lane, rm. 1061
Rockville, MD 20993-0002

Re: Docket No. FDA-2013-N-0577: Agency Information Collection Activities; Proposed Collection; Comment Request; Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format; 78 Fed. Reg. 104 (May 30, 2013)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in response to the Food and Drug Administration's (FDA's) proposed collection of information: requirements for submission of labeling for human prescription drugs and biologics in electronic format. PhRMA is a voluntary, non-profit association that represents the country's leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested approximately $550 billion in the search for new treatments and cures, including an estimated $48.5 billion in 2012 alone.

PhRMA member companies are committed to the use of information technology (IT) to improve the quality and efficiency of the regulatory review process. To that end, PhRMA member companies have been leaders in the early adoption and use of standardized formats for electronic submission of information to the Agency. Further, PhRMA and its member companies are committed to the successful implementation of PDUFA V IT Goals and continue to encourage FDA's improvement of the exchange, review and management of human drug and biologic applications throughout the product life cycle through strategic investments in automated, standards-based IT.

General Comments

- The Electronic Submission Gateway (ESG) for electronic submission of information to the Agency must not only be secure, but must also be stable and reliable.

- As the FDA and Industry move to a fully electronic environment with data standards requirements, it is important that the FDA approach information in a consistent, non-redundant manner (e.g., reviewers should not request paper copies of electronic submissions or submission/resubmission of documents in different electronic formats).

Specific Comments regarding FDA's proposed information collection:

1. ***The proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility.***

    - In general, PhRMA agrees that the electronic submission of the content of labeling in Structured Product Labeling (SPL) format is necessary for the proper performance of FDA's functions and that the information has practical utility for FDA and Industry by providing consistent format standards. Additionally the use of SPL allows for consistent, publicly accessible product labeling information on Daily Med.

2. ***The accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used.***

    Currently, SPL is created in multiple manners across industry including the internal creation of SPL by skilled employees within the sponsor organization as well as sponsors leveraging specialty vendors to build compliant SPL files for submission to the agency.

    Creation of SPL

    As stated in the Federal Register Notice, the time estimate of 1.25 hours appears to be based solely upon the time for conversion from MS Word or PDF to SPL.

    - Estimates from PhRMA member companies (who typically convert an MS Word or PDF document to SPL) vary from 4 to 12 hours for experienced users developing the initial well-formed SPL and 4-5 hours for an SPL update. These times may vary depending on the complexity of the labeling metadata (e.g., number of formulations of the product). This time can be longer if the SPL is rejected by the Agency and changes are necessary.

    - The amount of time required for the validation of the SPL XML file has not been addressed. While the validation itself would take a short amount of time, the

adjudication of any issues encountered adds time to this estimate. Another requirement that is not included in the estimate is the need for the use of at least one XML validation tool to ensure the SPL file set is well-formed and error-free prior to submission to the agency. The 1.25 hour estimate in the Federal Register notice does not take into account the two-part validation approach necessary for a submission– to ensure that the submission is well-formed and to ensure that it passes the FDA validation tool.

- With regard to the process that the agency describes in the Federal Register notice regarding the creation of SPL by copying table cells to create an SPL file is time consuming and prone to errors due to the manual nature of the work. It is PhRMA member companies experience that software tools do not allow users to copy and paste the text and render it as intended in the SPL. Most users need to apply applicable formatting to tables, which leads to longer conversion timelines. Considering the time to manually create the SPL file and then conduct a proof-read (QC) of the document, we would anticipate these activities would exceed 1.25 hours to complete the process.

Burdens that have not been reflected in calculations

- Sponsors experience challenges with maintaining multiple formats of labeling including the adjudication of comments from the agency and documenting agreements to final labeling during labeling negotiations. Maintaining these multiple formats of labeling is an additional burden on sponsors.
    - It is challenging to update the SPL file for submission when a non-annotated or partially annotated MS Word document from FDA is received as it requires a significant amount of time to identify where the changes are within the document.
    - Although SPL is a useful and necessary format for FDA, it typically involves the extra time and costs of conversion from another format, especially since it is recommended by FDA to submit documents in both MSWord and SPL.[1]
    - There are costs associated with staying current with changes in terminology and software versions for SPL.

- Cost of digital certificate – We note that while this cost is accounted for in drug establishment registration and listing requirements, OMB approval for this collection of information expired last year.[2]

- Cost of duplicate certificates from different vendors

[1] See lines 109-111 in Draft Guidance for Industry: SPL Standard for Content of Labeling Technical Qs & As. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

[2] http://www.reginfo.gov/public/do/PRAOMBHistory?ombControlNumber=0910-0045#

- As noted in the Federal Register on May 30, 2013, a digital certificate is needed to use the ESG and a fee is charged for the digital certificate. Registrants may need to renew the certificate not less than annually. Earlier this year, PhRMA became aware of member companies receiving messages from FDA that VeriSign/Symantec certificates, a vendor listed on FDA.gov as an approved vendor for certificates, were not acceptable for use for submissions to the FDA via the ESG. As a result, sponsors purchased multiple certificates from different vendors in order to use the ESG. PhRMA believes that the FDA's maintenance of an accurate list of acceptable vendors for digital certificates that is communicated to stakeholders via a formal process with appropriate notice of change (e.g., Notice in the Federal Register with one year notice of changes to the list of accepted certificates) is a straightforward way to minimize the burden of the collection of information on respondents.

3. Ways to enhance the quality, utility, and clarity of the information to be collected

- MS Word with track changes continues to be the primary format used during labeling negotiations between the sponsor and FDA. MS Word is a quick and efficient means to capture the labeling discussions between the sponsor and FDA. The expectation is usually that the sponsor submits the MS Word version to the agency to confirm the dialogue from the labeling negotiations. These documents are typically red-lined to indicate the changes. In its current form, SPL does not provide a red-lined view of the changes of labeling discussed. Additionally, submissions of the label based on discussions between the sponsor and agency are expected on short turn-around (submission windows are typically less than 24 hours) and these submissions are best facilitated by MS Word and not SPL.

4. Ways to minimize the burden of the collection of information on respondents

- Until the FDA is able to negotiate labels using SPL only, the FDA could leverage the burden on Sponsors by not requiring SPL until 14 days post-approval.
- Provide clear guidance to industry in order to determine what labeling format is necessary and when so that the industry can provide cost efficient and timely SPL to address FDA's needs.
- FDA's use of a single, electronic file format (SPL) for receipt, review and revision of labeling. PhRMA member companies report receiving information from FDA during the review of labeling in many formats, including MS Word (both editable and hard-formatted), faxes, texts, in emails, or other scanned documents with hand-written comments.
- Reduce FDA's requests for submission of both SPL and MS Word file for labeling. There is additional burden on industry when multiple formats are requested and used by the FDA for label revisions.

- Document management (e.g., version control, tracking changes, QC, validation, etc.) of the MS Word documents.
- Depending on the submission format, each iteration of the MS Word document may need to be converted to SPL for submission (this includes the time to convert, QC, validate, etc. the SPL). Essentially managing the same activities for two different formats doubles the work load and causes incremental costs to be incurred by sponsors; this is multiplied for an NDA or ANDA with more than one content of labeling.

Conclusion

PhRMA appreciates the opportunity to provide comments on FDA's proposed collection of information, and we would be happy to discuss our comments with the Agency in more detail. If you have any questions, please do not hesitate to contact us.

Respectfully Submitted,

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