Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format

OMB Control Number 0910-0530

SUPPORTING STATEMENT

Terms of Clearance: None

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA is requesting that OMB extend approval under the Paperwork Reduction Act (44 USC 3501-3520) for the information collection resulting from the requirement that the content of labeling for prescription drug products be submitted to FDA electronically in a form that FDA can process, review, and archive. This requirement was set forth in the final rule entitled "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format" (December 11, 2003; 68 FR 69009), which amended FDA regulations governing the format in which certain labeling is required to be submitted for FDA review with new drug applications (NDAs) (21 CFR 314.50(l)(1)(i)), including supplemental NDAs, abbreviated new drug applications (ANDAs) (21 CFR 314.94(d)(1)(ii)), including supplemental ANDAs, and annual reports (21 CFR 314.81(b)(2)(iii)(b)) (the final rule also applied to certain BLAs, but the information collection for these requirements is not part of this OMB approval request).

2. Purpose and Use of the Information Collection

Each year FDA conducts a word-for-word comparison as part of the review process for more than 1,000 proposed labeling changes for approved NDAs and BLAs, and more than 2,600 proposed original and supplemental labeling changes for ANDAs. Conducting these comparisons manually using two paper copies of the labeling is a slow

process and subject to error. Requiring the electronic submission of labeling for NDAs, certain BLAs, ANDAs, supplements, and annual reports greatly enhances the accuracy and speed of labeling review. This results in increased protection of the public health because electronic review and comparison of labeling files provides a higher degree of certainty that all sections of prescription drug labeling are correct.

3. Use of Improved Information Technology and Burden Reduction

In May 2009, FDA issued a guidance for industry entitled "Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Listing." The guidance describes how to electronically create and submit structured product labeling (SPL) files using defined code sets and codes for establishment registration and drug listing information, including labeling. This guidance currently covers FDA's preferred process for submitting the content of labeling in electronic format. In addition, FDA has issued other guidance's on electronic submissions at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm.

4. Efforts to Identify Duplication and Use of Similar Information

The requirement to submit the content of labeling electronically is in addition to existing requirements that paper copies of the label and labeling and specimens of enclosures be submitted. However, requiring the electronic submission of the content of labeling greatly enhances the accuracy and speed of labeling review by FDA. This results in increased protection of the public health because electronic review and comparison of labeling files provides a higher degree of certainty that all sections of prescription drug labeling are correct.

5. Impact on Small Businesses or Other Small Entities

Although new drug development is typically an activity completed by large multinational drug firms, the information collection requested under the guidance applies to small as well as large companies. Under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

The content of labeling is required to be submitted electronically for review with NDAs, certain BLAs, ANDAs, supplements, and annual reports. FDA's review of labeling is an integral part of its approval of marketing application for drugs and biologics. The labeling must be consistent with the approved conditions for marketing.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

There are no special circumstances for this collection of information.

8. Comments In Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of May 30, 2013 (78 FR 32392). We received two comments. Both comments disagreed with FDA’s estimate of 1.25 hours for converting the content of labeling to SPL format. One comment said it would take 4 to 12 hours for experienced users to develop the initial well-formed SPL and 4-5 hours for an SPL update, and that these estimates vary depending on the complexity of the labeling metadata and whether changes are necessary. The comment said that FDA also needs to account for the time required for validating the SPL XML file, including the need for using at least one XML validation tool to ensure that the SPL file set is well-formed and

error-free. The comment said that copying table cells to create an SPL file is time consuming and prone to errors, and that software tools do not allow users to copy and paste the text and render it as intended in SPL. The comment said that most users need to apply applicable formatting to tables, which leads to longer conversion timelines, and that manually creating the SPL file and proofing the document is time-consuming.

One comment said that updating the SPL file for submission to FDA when a non-annotated or partially annotated MS Word document is received from FDA requires a significant amount of time to identify the changes to the labeling. The comment said that although SPL is a useful and necessary format it involves extra time and costs for staying current with changes in terminology and software versions, and for conversion from another format when FDA requests documents in both MS Word and SPL. The comment said that maintaining multiple formats of labeling, negotiating FDA comments, and documenting agreements to final labeling is time-consuming.

A comment requested that FDA use a single, electronic file format for receipt, review, and revision of labeling. The comment said that companies currently receive information from FDA during its 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. The comment noted that each iteration of the MS Word document may need to be converted to SPL for submission, and that managing the same activities for two different formats doubles the work-load and causes incremental costs to be incurred by companies. The comment also said that there should be better document management (e.g., version control, tracking changes, and validation)

of the MS Word documents. A comment said that the staffing, expertise, and technical support necessary to independently determine the need for a labeling change is costly.

One comment preferred the use of MS Word for labeling revisions and negotiations with FDA, and said that until FDA is able to revise labeling using only SPL it should not require an SPL submission until 14 days post-approval.

Concerning the need for a digital certificate to use the ESG, one comment said that companies may need to renew the certificate "not less than annually." The comment said that FDA should maintain an accurate list of acceptable digital certificate vendors and communicate the list to stakeholders via a formal process, as well as issue appropriate notice of changes. The comment noted that some companies received messages from FDA that one of the vendors listed as an approved certificate vendor was not acceptable for use for submissions to FDA, and, as a result, the companies purchased multiple certificates from different vendors in order to use the ESG.

A comment requested clarification concerning the type of filing needed or anticipated by FDA to make an appropriate labeling decision. The comment said that the FEDERAL REGISTER notice is not clear about what type of filing is needed "other than a CBE, which will not allow the Agency adequate time to review if the label change is solely linked to one manufacturer or if it is indeed a product related safety concern applicable to an entire class of pharmaceuticals."

FDA appreciates the comments. We will respond to the issues raised in the comments and amend this collection if necessary as soon as we have gathered sufficient information to address the cost issues specified in the comments. The public will have an opportunity to comment on our response at that time.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this guidance.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under these regulations is protected under 21 CFR 314.430, 21 CFR 601, and 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden and Costs

12a. Annualized Hour Burden Estimate –

This OMB approval request is only for the burden associated with the electronic submission of the content of labeling. The burden for submitting labeling as part of NDAs, ANDAs, supplemental NDAs and ANDAs, and annual reports, has been approved by OMB under Control Number 0910-0001.

We estimate that it should take applicants approximately 1.25 hours to convert the content of labeling from Word or PDF to SPL format. The main task involved in this conversion is copying the content from one document (Word or PDF) to another (SPL). Over the past few years, several enhancements have been made to SPL authoring software which significantly reduces the burden and time needed to generate well-formed SPL documents. SPL authors may now copy a paragraph from a Word or PDF document and paste the text into the appropriate section of an SPL document. In those cases where

an SPL author needs to create a table, the table text may be copied from the Word or PDF document and pasted into each table cell in the SPL document, eliminating the need to retype any information. Enhancements have also been made to the software for conversion vendors. Conversion software vendors have designed tools which will import the Word version of the content of labeling and, within minutes, automatically generate the SPL document (a few formatting edits may have to be made).

Based on the number of content of labeling submissions received during the past few years, we estimate that approximately 5,750 content of labeling submissions are made annually with original NDAs, ANDAs, supplemental NDAs and ANDAs, and annual reports by approximately 500 applicants. Therefore, the total annual hours to convert the content of labeling from Word or PDF to SPL format would be approximately 7187.50 hours.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Content of labeling submissions in NDAs, ANDAs, supplemental NDAs and ANDAs, and annual reports	500	11.50	5,750	1.25	7,187.50

12b. Annualized Cost Burden Estimates –

FDA has estimated an average industry wage rate of $75.00 per hour for preparing and submitting the information collection requirements under OMB Control Number 0910-0001. Using the average wage rate of $75.00 per hour, and multiplied

times the total hour burden estimated above, the total cost burden to respondents is $539,062.50.

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
NDA applicants	7,187.50	$75	$539,062.50

13. Estimates of Other Total Annual Cost Burden to Respondents and Recordkeepers/Capital Costs

We conclude that there are no capital costs or operating and maintenance costs associated with this collection of information. In May 2009, FDA issued a guidance for industry entitled "Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Listing." The guidance describes how to electronically create and submit SPL files using defined code sets and codes for establishment registration and drug listing information, including labeling. The information collection resulting from this guidance, discussed in the Federal Register of January 8, 2009 (74 FR 816), has been approved by OMB under Control Number 0910-0045. As discussed in the January 8, 2009, Federal Register notice, to create an SPL file and submit it to FDA, a registrant would need the following tools: A computer, appropriate software, access to the Internet, knowledge of terminology and standards, and access to FDA's electronic submission gateway (ESG). Registrants (and most individuals) have computers and Internet access available for their use. If a business does not have an available computer or access to the Internet, free use of computers and the Internet are usually available at public facilities, e.g., a community library. In addition, there should be no additional costs associated with obtaining the appropriate software. In 2008, FDA collaborated with GlobalSubmit to make available free SPL authoring software that SPL authors may utilize to create new SPL documents or edit previous versions. (Information on obtaining

this software is explained in section IV.A of the guidance "Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Listing.") In addition to the software, FDA also provides technical assistance and other resources, code sets and codes, and data standards regarding SPL files.

After the SPL file is created, the registrant would upload the file through the ESG, as explained in the January 8, 2009, Federal Register notice. A digital certificate is needed to use the ESG. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents. A fee of up to $20.00 is charged for the digital certificate and the registrant may need to renew the certificate not less than annually. We are not calculating this fee as a cost for this extension because all applicants who submit content of labeling are also subject to the drug establishment registration and listing requirements and would have already acquired the digital certificate as a result of the May 2009 guidance on drug establishment registration and listing.

14. Annualized Cost Burden to the Federal Government

There are no significant additional FDA reviewer costs resulting from this requirement because the labeling is submitted as part of already required submissions related to the application approval process, as approved under OMB Control Numbers 0910-0001 and 0910-0572.

15. Explanation for Program Changes or Adjustments

The changes in burden are the result of a re-calculation based on the current number of content of labeling submissions.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no plans for tabulation and publication and project time schedule.

17. Reasons Display of OMB Expiration Date is Inappropriate

The agency is not seeking to display the expiration date for OMB approval of the information collection.

18. Exception to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.