SUPPORTING STATEMENT

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

A. Justification

1. Circumstances of Information Collection

This information collection approval request is for Food and Drug Administration (FDA) regulations finalized in a final rule entitled "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format" (December 11, 2003; 68 FR 69009) (the final rule). The final rule amended FDA regulations governing the format in which certain labeling is required to be submitted for review with new drug applications (NDAs), certain biological license applications (BLAs), abbreviated new drug applications (ANDAs), supplements, and annual reports. The final rule required the electronic submission of the content of labeling (i.e., the content of the package insert or professional labeling, including all text, tables, and figures) in NDAs, certain BLAs, ANDAs, supplements, and annual reports electronically in a form that FDA can process, review, and archive. The form that FDA can accept for processing, reviewing, and archiving under the final rule is portable document format (PDF). The requirement to submit the content of labeling electronically was in addition to existing requirements that copies of the label and labeling and specimens of enclosures be submitted.

2. Purpose and Use of Information

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. Because reviewers currently conduct these comparisons manually using two paper copies of the labeling, the process is slow 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

Although FDA has not previously required regulatory submissions in electronic format, the agency has issued several guidances describing how to make voluntary electronic submissions to the agency. In January 1999, FDA issued a guidance on general considerations for electronic submissions entitled “Providing Regulatory Submissions in Electronic Format--General Considerations.” The general considerations guidance included a description of the types of electronic file formats that we are able to accept for processing, reviewing, and archiving electronic documents. In January, 1999, FDA announced the availability of a guidance entitled “Providing Regulatory Submissions in Electronic Format--NDAs,” which provided information on how to submit a complete archival copy of an NDA in electronic format. In November 1999, FDA published a guidance to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license

application (ELA). Among the more recent guidances are the guidance for ANDAs, “Providing Regulatory Submission in Electronic Format–-ANDAs” (June 27, 2002), and “Providing Regulatory Submission in Electronic Format–- Annual Reports for NDAs and ANDAs" (August 2003).

4. Efforts to Identify Duplication

The requirement to submit the content of labeling electronically is in addition to existing requirements that 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. Involvement of 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 If Information Collected 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. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

There is no inconsistency resulting from this final rule.

8. Consultation Outside the Agency

The final rule was proposed May 3, 2002. We received thirteen sets of written comments on the proposed rule from manufacturers, trade associations, advocacy groups, consulting firms, and individuals. The majority of the comments supported FDA's proposal to require that the content of certain labeling be submitted electronically in a form that FDA can process, review, and archive. A few comments requested clarification on various aspects of the rule, and one comment opposed the exemptions from specific controls under part 11. The final rule contained a summary of the comments received and the agency's responses.

In the Federal Register of March 29, 2006 (71 FR 15752), we gave interested parties an opportunity to comment on the information collection during the process requesting that OMB extend approval of the collection. We received several comments. Generally, the comments said that, unlike FDA's December 11, 2003, final rule, the agency has now identified Extensible Markup Language (XML) as the required file format for Structured Product Label documents (SPL). The comments said that the March 29, 2006, Federal Register notice does not take into account the amount of time required to obtain, install, and update the program required to create the electronic files in the new format, and that

SPL is a relatively new format requiring an initial investment in software, training, and process change that cannot simply be converted from the Word or PDF version of labeling. The comments said that the process for creating the SPL labeling includes significant effort in mapping, coding, recreation of the file, and quality control.

We appreciate the comments and believe they raise important issues. We will respond to the comments and amend this collection as soon as we have gathered sufficient information to address the costs specified in the comments. The public will have an opportunity to comment on our response at that time.

9. Remuneration of Respondents

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

10. Assurance of Confidentiality

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. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Copies of product labeling have been required to be submitted to FDA for review in NDAs, certain BLAs, ANDAs, certain supplements, and annual reports under §§ 314.50,

314.70, 314.81, 314.94, 314.97, 314.98, 601.2, and 601.12. Under these regulations, copies of labeling may be submitted electronically or on paper. The final rule added the requirement to submit the content of labeling in electronic format to simplify the drug labeling review process and speed up the approval of labeling changes. The reporting burden for submitting labeling under §§ 314.50, 314.70, 314.81, 314.94, 314.97, and 314.98 has been estimated by FDA and the collection of information has been approved by OMB under OMB control number 0910-0001, most recently until May 31, 2008. The reporting burden associated with current §§ 601.2 and 601.12 has also been estimated and this collection of information has been approved by OMB under OMB control number 0910-0338, most recently until September 30, 2008. We are not re-estimating these approved burdens in this action. Only the additional re-occurring reporting burdens associated with the electronic submission of the content of labeling in the final rule are estimated in this action.

New NDAs (§ 314.50), ANDAs (§ 314.94), and BLAs (§ 601.2): Based on the number of submissions during 2005 under the approved collections of information for §§ 314.50, 314.94, and 601.2, we estimate that approximately 75 NDA applicants, 160 ANDA applicants, and 6 BLA applicants (respondents) submit applications to us annually. We

estimate that these applicants (respondents) submit approximately 111 NDAs, 766 ANDAs, and 21 BLAs each year that are subject to the requirements of the final rule. As explained in the Paperwork Reduction Act section of the final rule, we estimate that the hours per response, i.e., the additional time necessary for submission of the content of labeling in electronic format for these applications, will be less than 15 minutes.

Supplements to NDAs (§ 314.70), ANDAs (§ 314.97), and BLAs (§ 601.12(f)(1) and (f)(2)): Based on the number of submissions during 2005 under the approved collections of information for §§ 314.70, 314.97, and 601.12(f)(1) and (f)(2), we estimate that approximately 272 NDA applicants, 189 ANDA applicants, and 35 BLA applicants (respondents) submit supplements to approved applications to us annually. We estimate that these applicants (respondents) submit approximately 1,839 NDA supplements, 3,208 ANDA supplements, and 82 BLA supplements each year that are subject to the requirements of the final rule. As explained in the Paperwork Reduction Act section of the final rule, we estimate that the hours per response, i.e., the additional time necessary for submission of the content of labeling in electronic format for these applications, will be less than 15 minutes.

Annual Reports for NDAs (§ 314.81), ANDAs (§ 314.98), and BLAs (§ 601.12(f)(3)): Based on the number of submissions during 2005 under the approved collections of information for §§ 314.81, 314.98, and 601.12(f)(3), we estimate that approximately 306 NDA applicants, 333 ANDA applicants, and 4 BLA applicants (respondents) submit annual reports to us annually. We estimate that NDA applicants submit to us approximately 2,617 annual reports, ANDA applicants submit approximately 6,054 annual reports, and BLA applicants submit approximately 16 annual reports each year that are subject to the requirements of the final rule. As explained in the Paperwork Reduction Act section of the final rule, we estimate that the hours per response, i.e., the additional time necessary for submission of the content of labeling in electronic format for these submissions, will be less than 15 minutes.

FDA requests OMB approval for the following information collection:

Table 1. – Estimated Annual Reporting Burden

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
New Applications:					
■ 314.50	75	1.48	111	.25	27.75
■ 314.94	160	4.79	766	.25	191.50
■ 601.14[1]	6	3.50	21	.25	5.25
Supplements:					
■ 314.70	272	6.76	1,839	.25	459.75
■ 314.97	189	16.98	3,208	.25	802
■ 601.14[2]	35	2.34	82	.25	20.5
Annual Reports:					

■ 314.81	306	8.55	2,617	.25	654.25
■ 314.98	333	18.18	6,054	.25	1,513.50
■ 601.14[3]	4	4	16	.25	4
Total Reporting Burden Hours:					**3,678.50**

Note: There are no operating and maintenance costs or capital costs associated with this collection of information.

1. Applications submitted under § 601.2
2. Supplements submitted under § 601.12(f)(1) and (f)(2)
3. Annual reports submitted under § 601.12(f)(3)

13. Estimates of Annualized Cost Burden to Respondents

FDA has estimated an average industry wage rate of $50.00 per hour for preparing and submitting the information collection requirements under OMB Control Number 0910-0001. Using the averaged wage rate of $50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is $ 183,925 (3,678.50 x $50).

14. Estimates of Annualized Cost Burden to the 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. Changes In Burden

The changes in burden from the final rule are the result of more recent data submissions, and the elimination of one-time costs in the Paperwork Reduction Act section of the final rule.

16. Time Schedule, Publication, and Analysis Plans

There are no publications.

17. Displaying of OMB Expiration Date

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

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.

PAPERWORK REDUCTION ACT SUBMISSION

Please read the instructions before completing this form. For additional forms or assistance in completing this form, contact your agency's Paperwork Clearance Officer. Send two copies of this form, the collection instrument to be reviewed, the supporting statement, and any additional documentation to: Office of Information and Regulatory Affairs, Office of Management and Budget, Docket Library, Room 10102, 725 17th Street NW, Washington, DC 20503.

1. Agency/Subagency originating request FDA	2. OMB control number b. [x] None a. 0910 -0530
3. Type of information collection (*check one*) a. [ ] New Collection b. [ ] Revision of a currently approved collection c. [X] Extension of a currently approved collection d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired f. [ ] Existing collection in use without an OMB control number For b-f, note Item A2 of Supporting Statement instructions	4. Type of review requested (*check one*) a. [x] Regular submission b. [ ] Emergency - Approval requested by at close of comment period c. [ ] Delegated 5. Small entities Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No 6. Requested expiration date a. [X] Three years from approval date b. [ ] Other Specify:____/
7. Title Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format	
8. Agency form number(s) (*if applicable*)	
9. Keywords sponsors, drugs. clinical investigation	
10. Abstract This guidance discusses how the agency will implement a pilot program for frequent scientific feedback and interactions between FDA and applicants during the investigational phase of development of certain Fast Track drug and biological products. Applicants are being asked to apply to participate in the Pilot 2 program.	
11. Affected public (*Mark primary with "P" and all others that apply with "x"*) a. ___ Individuals or households d. ___ Farms b. _x__ Business or other for-profit e. ___ Federal Government c. ___ Not-for-profit institutions f. ___ State, Local or Tribal Government	12. Obligation to respond (*check one*) a. [ ] Voluntary- (guidance document) b. [X] Required to obtain or retain benefits c. [ ] Mandatory
13. Annual recordkeeping and reporting burden a. Number of respondents _____	14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)*

b. Total annual responses _____ 1. Percentage of these responses collected electronically 100 % c. Total annual hours requested 3,678.50 ____ d. Current OMB inventory 52,344 _____ e. Difference 48,665.50 ____ f. Explanation of difference 1. Program change _____ 2. Adjustment more recent data submissions, and the elimination of one-time costs _____	a. Total annualized capital/startup costs 0 b. Total annual costs (O&M) 0 c. Total annualized cost requested 0 d. Current OMB inventory 0 e. Difference 0 f. Explanation of difference 1. Program change _____ 2. Adjustment _____
15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*) a. __ Application for benefits e.__ Program planning or management b. __ Program evaluation f.__ Research c. __ General purpose statistics g. x Regulatory or compliance d. __ Audit	16. Frequency of recordkeeping or reporting *(check all that apply)* a. [ ] Recordkeeping b. [ ] Third party disclosure c. [x] Reporting 1. [x] On occasion 2. [ ] Weekly 3. [ ] Monthly 4. [ ] Quarterly 5. [ ] Semi-annually 6. [ ] Annually 7. [ ] Biennially 8. [ ] Other (describe) _____
17. Statistical methods Does this information collection employ statistical methods [ ] Yes [x] No	18. Agency Contact (person who can best answer questions regarding the content of this submission) Name: Karen Nelson Phone: 827-1482