SUPPORTING STATEMENT
Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Pregnancy and Lactation Labeling – Proposed Rule

A. Justification

1. Circumstances of Information Collection

The proposed rule would amend FDA regulations concerning the format and content of the "Pregnancy," "Labor and Delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drugs. The proposal would require that labeling include a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling would also include relevant clinical information to help health care professionals make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X. The "Labor and Delivery" subsection would be eliminated because information on labor and delivery would be included in the "Pregnancy" subsection. The proposed rule is intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that will be useful for decision-making by women of childbearing age and their health care providers.

Under proposed §§ 201.57(c)(9)(i) and 201.57(c)(9)(ii), holders of approved applications would be required to provide new labeling content in a new format – that is, to completely rewrite the pregnancy and lactation portions of each drug's labeling. These application holders would be required to submit supplements requiring prior approval by FDA before distribution of the new labeling, as required in § 314.70(b) or § 601.12(b). Under proposed § 201.80(f)(6)(i), holders of approved applications would be required to remove the pregnancy category designation (e.g., "Pregnancy Category C") from the "Pregnancy" subsection of the "Precautions" section of the labeling. These application holders would report the labeling change in their annual report, as required in § 314.70(d) or § 601.12(d).

The new content and format requirements of the proposed rule would apply to all applications that are required to comply with the PLR, including: (1) applications submitted on or after the date the proposed rule becomes final; (2) applications pending on the date the proposed rule becomes final; and (3) applications approved from June 30, 2001, to the effective date of the pregnancy labeling rule.

Information collection subject to the PRA would consist of the following submissions under the proposed rule:

(1) Applications submitted on or after the effective date of the proposed rule (§§ 314.50; 314.70(b); 601.2; 601/12(b)).

(2) Amendments to applications pending on the effective date of

the final rule (§ 314.60).

(3) Supplements to applications approved from June 30, 2001, to the effective date of the final rule (§ 314.70(b); 601.12(b)).

(4) Holders of applications approved before June 29, 2001, that contain a pregnancy category would be required to remove the pregnancy category designation by 3 years after the effective date of the final rule and include this labeling change in their annual report (§ 314.70(d, 601.12(d)).

2. Purpose and Use of Information

The pregnancy category system has been criticized as being confusing and overly simplistic. The standardized statements required by current regulations do not distinguish information about risk alone from judgments based on both risk and benefit. In addition, the statements associated with the pregnancy categories do not take into account that a woman may already have been exposed to a drug before learning she is pregnant, and thus considerations for her may differ from those for a women who has not yet been exposed to a drug during pregnancy. The agency believes that advice and cautions about drug use should be clear and should specifically relate to the particular clinical situation, which includes whether exposure has already occurred or is being contemplated. The clinical situation

also includes the risks presented if the woman has a condition or disease that remains untreated during her pregnancy.

3. Use of Improved Information Technology

The drug product labeling affected by this rule is submitted to FDA for approval as part of the NDA, ANDA, BLA or an amendment or supplement to an application. FDA has undertaken many initiatives to improve information technology used to submit these applications to the agency.

In the Federal Register of December 11, 2003, FDA issued a final rule amending FDA regulations governing the format in which certain labeling is required to be submitted for review with NDAs, certain BLAs, ANDAs, supplements, and annual reports. The final rule requires 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 agency views this final rule on content and format of labeling as an essential step toward the success of its electronic labeling initiative. The labeling format required by this rule for new and more recently approved products should facilitate transition to an electronic format.

The following guidances for industry have been developed to

improve the use of information technology in the submission of marketing applications for human drugs and related reports:

- "Providing Regulatory Submissions in Electronic Format--NDAs" (January 28, 1999). This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs.
- "Providing Regulatory Submissions in Electronic Format--General Considerations" (January 28, 1999). This guidance includes a description of the types of electronic file formats that the agency is able to accept to process, review, and archive electronic documents. The guidance also states that documents submitted in electronic format should enable the user to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents.
- "Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format" (November 12, 1999). This guidance provides information 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).

• "Providing Regulatory Submissions in Electronic Format-—Prescription Drug Advertising and Promotional Labeling" (January 31, 2001). This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

• "Providing Regulatory Submissions in Electronic Format-—ANDAs" (June 27, 2002). This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

• "Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs" (August 2003). This guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

• "Providing Regulatory Submissions in Electronic Format-—Postmarketing Periodic Adverse Drug Experience Reports" (June 2003). This guidance discusses general issues related the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

• "Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs" (August, 2003). This draft guidance discusses issues related to the electronic submission of annual reports, for NDAs and ANDAs.

• "Providing Regulatory Submissions in Electronic Format-—Human

Pharmaceutical Product Applications and Related Submissions" (August 2003). This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional material.

• "Providing Regulatory Submissions in Electronic Format-–General Considerations" (October 2003). This draft guidance discusses general issues common to all types of electronic regulatory submissions.

• "Providing Regulatory Submissions in Electronic Format-–Content of Labeling" (February 2004). This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication

This information is not otherwise submitted to the agency, and thus, there is no duplicate reporting.

5. Involvement of Small Entities

As explained in the “Analysis of Economic Impacts” section of the proposed rule, the proposed rule is unlikely to have a

significant impact on a substantial number of small entities.

6. Consequences If Information Collected Less Frequently

The labeling that would be required by this rulemaking is submitted under existing regulatory procedures and timeframes. It is important that labeling include a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. Also important is relevant clinical information to help health care professionals make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The proposed rule is intended to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that will be useful for decision-making by women of childbearing age and their health care providers.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

None of the collection requirements are inconsistent with 5 CFR 1320.5(d)(2).

8. Consultation Outside the Agency

As explained in the proposed rule, FDA has held hearings and conducted focus groups in developing the proposed labeling changes. In addition, the public will have the opportunity to comment on the

proposed rule. All comments will be summarized and responded to in the final rule.

9. Remuneration of Respondents

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

10. Assurance of Confidentiality

Confidentiality of information submitted under the drug approval process is safeguarded under § 314.430.

11. Questions of a Sensitive Nature

This information collection does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Hour Burden

The information collection requirements and burden estimates are summarized in the table below. Based on data provided in the "Analysis of Economic Impacts" section of the proposed rule, FDA estimates that approximately 1,613 applications (1,613 includes approximately 1,197 innovator and 416 generic drug products)

containing labeling consistent with this rulemaking would be submitted to FDA by approximately 885 applicants. Based on data provided in section VIII of this document, FDA estimates that it would take applicants approximately 20 hours to prepare and submit labeling consistent with this rulemaking. The estimate of 20 hours is incremental, in that it applies only to the requirements for this rulemaking and does not indicate the total hours required to prepare and submit complete labeling for these applications. The information collection burden to prepare and submit labeling in accordance with §§ 201.56, 201.57, and 201.80 is approved by OMB under Control Number 0910-0572.

FDA also estimates that approximately 111 amendments to applications pending on the effective date of the final rule would be submitted to FDA as a result of this proposal, by approximately 81 applicants, and that it would take those applicants approximately 20 hours (incremental) to prepare and submit each amendment.

In addition, FDA estimates that approximately 1,789 supplements to approved applications would be submitted to FDA to update labeling in accordance with this proposal, that approximately 210 sponsors would submit these supplements, and that it would take those application holders approximately 85 hours (incremental) to prepare and submit each supplement (the estimate for innovator companies is approximately 85 hours, and the estimate for generic companies is

approximately 22 hours; for purposes of this information collection analysis, FDA used the higher estimate).

FDA also estimates that approximately 4,720 annual reports (4,720 includes approximately 1,697 innovator and 3,023 generic drug produsts) containing labeling changes resulting from this rulemaking would be submitted to FDA by approximately 300 application holders, and that it would take approximately 50 hours to prepare and submit those revisions (the estimates for innovator companies is approximately 50 hours, and the estimate for generic companies is approximately 22 hours; for purposes of this information collection analysis, FDA used the higher estimate).

FDA must request an extension of approval of this information collection every 3 years. For purposes of OMB approval for the first 3-year period, FDA divided the total hours in Table 12 (422,545 hours) by 3 to provide OMB an annualized estimate of burdens associated with this rulemaking (i.e., 140,848 hours).

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

Table 12 -- ESTIMATED REPORTING BURDEN[1]

Category (21 CFR section)	Number of Respondents	Number of Responses per Respon-dent	Total Responses	Hours per Response	Total Hours
New NDAs/ANDAs/BLAs/efficacy supplements submitted on or	885	1.82	1,613	20	32,260

after effective date (§§ 314.50; 314.70(b); 601.2; 601.12(b))					
Amendments to applications pending on effective date (§ 314.60)	81	1.37	111	20	2,220
Supplements to applications approved 6/30/01 to effective date (§ 314.70(b); 601.12(b))	210	8.52	1,789	85	152,065
Annual report submission of revised labeling for applications approved before 6/29/01 that contain a pregnancy category (§ 314.70(d); 601.12(d))	300	15.73	4,720	50	236,000
Grand Total					422,545
Annualized estimate: 422,545 ÷ 3 =					**140,848 Hours**

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

13. Estimates of Annualized Cost Burden to Respondents

Based on an industry hourly wage average cost of $50 per hour, the annual cost is as follows: Total burden hours of 140,848 @ $50 per hour equals $7,042,400.

14. Estimates of Annualized Cost Burden to the Government

Approximately 2 additional FTEs will be needed to review the labeling submitted under this proposed rule. If each FTE equals approximately $250,000, the cost to the government is approximately $ 500,000.

15. Changes in Burden

This request for OMB approval is for a proposed rule.

16. Time Schedule, Publication, and Analysis Plans

No comprehensive tabulation of the data is planned or anticipated.

17. Displaying of OMB Expiration Date

There are no forms in this collection.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, A 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. [ ] None

a. 0910 -

3. Type of information collection (*check one*)

a. [x] New Collection

b. [ ] Revision of a currently approved collection

c. [] 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 Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Pregnancy and Lactation Labeling – Proposed Rule

8. Agency form number(s) (*if applicable*)

9. Keywords human drugs labeling

10. Abstract The proposed rule would amend FDA regulations concerning the format and content of the “Pregnancy,” “Labor and Delivery,” and “Nursing mothers” subsections of the “Use in Specific Populations” section of the labeling for human prescription drugs.

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 – 885 _____

b. Total annual responses – 8,233_____

1. Percentage of these responses collected electronically – 100%

c. Total annual hours requested – 140,848____

d. Current OMB inventory – none; This is a proposed rule___

e. Difference _____

f. Explanation of difference

1. Program change _____

2. Adjustment _____

14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)*

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. [x] Annually

7. [ ] Biennially 8. [x] Other (describe) one-time

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: _____

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