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

[0910-NEW]

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section (under 21 CFR 201.57) and the "Precautions" section (under 21 CFR 201.80) of the labeling for human prescription drug and biological products. FDA is finalizing many of the provisions in the proposed rule issued on May 29, 2008 (73 FR 30831). The final rule is part of a broad effort by FDA to improve the content and format of prescription drug labeling. The final rule creates a consistent format for providing information about the risks and benefits of drug use during pregnancy and lactation and by females and males of reproductive potential. FDA's revisions to the content and format requirements for prescription drug and biological product labeling are authorized by the Federal Food, Drug, and Cosmetic Act (FD&C Act) and by the Public Health Service Act (PHS Act).

The final rule requires that the labeling subsections of certain drug products, the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery," be replaced by three subsections entitled "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." The final rule also requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

The final rule merges the current "Pregnancy" and "Labor and delivery" subsections into a single "Pregnancy" subsection of labeling. If there is a scientifically acceptable pregnancy exposure registry for the drug, the "Pregnancy" subsection must contain a specified statement about the existence of the registry, followed by contact information needed to enroll or to obtain information about the registry. FDA has concluded that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving data collection in pregnant women. Under "Pregnancy," the final rule also requires that the labeling include a summary of the risks of using a drug during pregnancy. If data demonstrate that a drug is not absorbed systemically, the "Risk Summary" must contain only a specified statement regarding this fact. If data demonstrate that the drug is absorbed systemically, the "Risk Summary" must include risk statements based on data from all relevant sources (human, animal, and/or pharmacologic), that describe, for the drug, the risk of adverse developmental outcomes.

The labeling must also contain relevant information, if it is available, to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy; this could include information on disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery. FDA believes that including such information supports health care providers' understanding of drug product risks and benefits and facilitates informed prescribing decisions and patient counseling. The labeling must also describe the data that are the basis for the risk statements and clinical information included in the "Pregnancy" subsection of labeling.

The final rule requires that the "Lactation" subsection of labeling contain a summary of the risks of using a drug during lactation. If data demonstrate that the drug is not absorbed systemically, this summary must contain only a specified statement regarding this fact. If data demonstrate that the drug is absorbed systemically by the mother, this summary must include, to the extent it is available, relevant information on the presence of the drug in human milk, effects of the drug on the breastfed child, and effects of the drug on milk production. For drugs absorbed systemically, a risk and benefit statement must appear at the end of the summary of risks, unless breastfeeding is contraindicated during drug therapy. FDA has determined that the inclusion of a risk and benefit statement will provide a useful framework for health care providers to use when making prescribing decisions for a lactating patient.

The "Lactation" subsection must also include, to the extent information is available, relevant information concerning ways to minimize drug exposure in the breastfed child in certain situations and concerning available interventions for monitoring or mitigating the adverse reactions presented elsewhere in the labeling. In addition, the labeling must also include pertinent information about the data that are the basis for the risk summary and clinical information included in the "Lactation" subsection of labeling.

FDA determined that because there was no consistent placement in the labeling of information about pregnancy testing, contraception, and infertility, it was difficult for health care providers to find this important information that can affect decision-making before or during pregnancy. Thus, the final rule requires that the "Females and Males of Reproductive Potential" subsection include relevant information when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that

suggest drug-associated fertility effects.

Through experience and stakeholder feedback, FDA learned that the pregnancy categories were confusing and did not accurately and consistently communicate differences in degrees of fetal risk. In addition, FDA learned that the pregnancy categories were heavily relied upon by clinicians but were often misinterpreted and misused in that prescribing decisions were being made based on the pregnancy category, rather than an understanding of the underlying information that informed the assignment of the pregnancy category. FDA believes that a narrative structure for pregnancy labeling, rather than a category system, is best able to capture and convey the potential risks of drug exposure based on animal or human data, or both. FDA has determined that retaining the pregnancy categories is inconsistent with the need to accurately and consistently communicate differences in degrees of fetal risk. Therefore, the final rule requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

2. Purpose and Use of the Information Collection

The final rule amends FDA regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. For human prescription drug and biological products subject to the Physician Labeling Rule (71 FR 3922, January 24, 2006), the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help

health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the "Labor and delivery" subsection because information about labor and delivery is included in the "Pregnancy" subsection. The final rule requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. The final rule creates a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential. These revisions will facilitate prescriber counseling for these populations.

3. Use of Improved Information Technology and Burden Reduction

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. In addition, FDA has issued several guidances for industry to improve the use of information technology in the submission of marketing applications for human drugs and related reports. These guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication and Use of Similar Information

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

5. Impact on Small Businesses or Other Small Entities

As explained in the "Analysis of Economic Impacts" section, FDA believes that the final rule is not a significant regulatory action under Executive Order 12866. However, because some small prescription drug manufacturers and prescription drug repackagers and relabelers will incur costs that total more than 1 percent of their annual income in some years, the FDA concludes that the final rule will have a significant economic impact on a substantial number of small entities.

6. Consequences of Collecting the Information Less Frequently

The labeling that is 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 final 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. 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

As explained in the final rule, FDA held hearings and conducted focus groups in developing this rulemaking. In addition, the public has had an opportunity to comment on the proposed rule, and all comments have been summarized and responded to in the final rule. As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995, FDA provided an opportunity for public comment on the information collection requirements of the proposed rule that published in the FEDERAL REGISTER of 5/29/2008 (73 FR 30831).

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 provision.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of information submitted under the drug approval process is safeguarded under 21 CFR 314.430.

11. Justification for Sensitive Questions

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 Burden Hours and Costs

12a. Annualized Hour Burden Estimate

The final rule amends FDA regulations concerning the content and format 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 final rule requires that labeling include, among other things, a summary of the risks of using a drug during pregnancy and lactation and a discussion of the data supporting that summary. The labeling also includes relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the current pregnancy categories A, B, C, D, and X. In addition, the "Labor and delivery" subsection has been eliminated because information on labor and delivery is included in the "Pregnancy" subsection. The final rule also requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. The final rule is intended to create a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential.

Under §§ 201.57(c)(9)(i) and 201.57(c)(9)(ii), holders of approved applications are required to provide new labeling content in a new format—that is, to rewrite the pregnancy and lactation portions of each drug's labeling. Under § 201.57(c)(9)(iii), these application holders are also required to include a new subsection 8.3, "Females and Males of Reproductive

Potential," which requires that when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects, this subsection must contain this information. These application holders are required to submit supplements requiring prior approval by FDA before distribution of the new labeling, as required in § 314.70(b) or § 601.12(f)(1).

Under § 201.80(f)(6)(i), holders of approved applications are 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 must report the labeling change in their annual reports, as required in § 314.70(d) or § 601.12(f)(3).

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

The following submissions under the final rule are subject to the PRA:

(1) Applications submitted on or after the effective date of the final rule (§§ 314.50; 314.70(b); 601.2; 601.12(f)(1));

(2) Amendments to applications pending on the effective date of the final rule (§§ 314.60; 601.2; 601.12(f)(1));

(3) Supplements to applications approved from June 30, 2001, to the effective date of the final rule (§§ 314.70(b); 601.12(f)(1));

(4) Annual reports for applications approved before June 30, 2001, that contain a pregnancy category, to report removal of the pregnancy category letter in their labeling (§§ 314.70(d), 601.12(f)(3)).

The information collection requirements and burden estimates are summarized in Tables 1 and 2 of this document. The burden estimates are based on data and timeframes used in the "Summary of Final Regulatory Impact Analysis" and for the final regulatory impact analysis of the final rule.

FDA estimates that approximately 4,000 applications containing labeling consistent with this rulemaking will be submitted to FDA during the 10-year period on or after the effective date of the final rule by approximately 390 applicants and repackagers and relabelers. The estimate of 4,000 applications includes labeling for approximately 800 applications submitted under section 505(b) of the FD&C Act or section 351 of the PHS Act, and 1,200 applications submitted under section 505(j) of the FD&C Act, and revised labeling from repackagers and relabelers for approximately 2,000 drug products. This estimate also includes labeling amendments submitted to FDA for applications pending on the effective date of the final rule. Based on data provided in section VII of this document and in the final regulatory impact analysis of the final rule, FDA estimates that for future approvals it will take applicants approximately 40 hours to prepare and submit labeling consistent with this rulemaking. The estimate of 40 hours applies only to the requirements of 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 Numbers 0910-0572 and 0910-0001.

In addition, FDA estimates that approximately 10,150 supplements to applications approved from June 30, 2001, to the effective date of the final rule, or pending on the effective date, will be submitted to FDA during the third, fourth, and fifth years after the effective date to update labeling in accordance with this final rule. This estimate includes approximately 1,080 NDA, BLA, and efficacy supplements, approximately 1,320 ANDA supplements, and labeling supplements from repackagers and relabelers for approximately 7,750 drug products. FDA estimates that approximately 390 application holders and repackagers and relabelers will submit these supplements, and that it will take approximately 120 hours to prepare and submit each supplement.

FDA also estimates that approximately 5,500 annual reports will be submitted to FDA during the third year after the effective date for applications approved before June 30, 2001, that contain a pregnancy category (5,500 includes annual reports for approximately 1,340 NDAs and BLAs and approximately 4,160 ANDAs containing labeling changes resulting from this rulemaking). FDA estimates that approximately 320 application holders will submit these annual reports, and that it will take approximately 40 hours for each submission.

As indicated in Tables 1 and 2 of this document, we estimate that the total hours resulting from the information collection in this rulemaking will be approximately 1,598,000 hours. The costs associated with this rulemaking, including labor costs, are discussed in section VII of this document and in the final regulatory impact analysis of the final rule.

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

Table 1.--Estimated Annual Reporting Burden

Type of Submission (21 CFR section)	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Supplements to applications approved 6/30/01 to effective date (§§ 314.70(b), 601.12(f)(1))	390	26	10,150 (Submitted 3rd, 4th, and 5th years after effective date)	120	1,218,000
Annual report submission of revised labeling for applications approved before 6/30/01 that contain a pregnancy category (§§ 314.70(d), 601.12(f)(3))	320	17	5,500 (Submitted 3rd year after effective date)	40	220,000
Total					1,438,000

Table 2--Estimated Annual Third-Party Disclosure Burden

Type of Submission (21 CFR section)	No. of Respondents	No of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
New NDAs/ANDAs/BLAs/efficacy supplements submitted on or after effective date, including amendments to applications pending on effective date (§§ 314.50, 314.60, 314.70(b), 601.2, 601.12(f)(1))	390	10	4,000 (Submitted during 10-year period after effective date)	40	160,000

12b. Annualized Cost Burden Estimate

As discussed in the "Summary of Final Regulatory Impact Analysis" and in the final regulatory impact analysis of the final rule, FDA estimates that over 10 years with a 7 percent discount rate, the present value of one-time costs of the rule equal $52.4 million and the present

value of the annual costs equal $14.4 million; with a 3 percent discount rate, the present value of one-time costs equal $60.1 million and the present value of the annual costs equal $18.2 million. The present value of the total costs equal $66.8 million with a 7 percent discount rate and $78.2 million with a 3 percent discount rate. The annualized costs of the rule total $9.5 million with a 7 percent discount rate and $9.1 million with a 3 percent discount rate.

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

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

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

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

No comprehensive tabulation of the data is planned or anticipated.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

There are no forms in this collection.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.