U.S. Food and Drug Administration
Content and Format of Labeling for
Human Prescription Drugs and Biologics;
Requirements for Pregnancy and Lactation Labeling

OMB Control No. 0910-0624

SUPPORTING STATEMENT **Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA) regulations. Specifically, regulations found at 21 CFR 201.57 governing the content and format of labeling requirements for "*Pregnancy*," "*Lactation*," and "*Females and Males of Reproductive Potential*" individuals. The regulations are intended to improve the content and format of prescription drug labeling by creating a consistent format for providing information about the risks and benefits of drug use during pregnancy and lactation by patients included within specific populations. The regulations also require the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

Under the "*Pregnancy*" subsection of the 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. We have concluded that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving data collection in pregnant women. 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. We believe 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 regulations require 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. We have 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.

Accordingly, we are requesting extension of OMB approval for the information collection found under 21 CFR 201.57 and discussed in this supporting statement.

2. Purpose and Use of the Information Collection

The information collection enables FDA to implement public health protection provisions under the Federal Food, Drug, and Cosmetic Act regarding the labeling of human prescription drugs and biologics. The applicable regulations require that product labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. They also establish 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.

3. Use of Improved Information Technology and Burden Reduction

The drug product labeling affected by these regulations 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. Agency regulations now require 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 as an essential step toward the success of its electronic labeling initiative. The labeling format required by these regulations 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

We are unaware of duplicative information collection, although we have established other collections supporting regulations at 21 CFR Part 201 including OMB Control No. 0910-0572 entitled "*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products.*" Because the instant collection was established as part of rulemaking and the regulations provide for a 10-year implementation schedule, we are retaining this collection to account for burden associated with the applicable regulatory requirements only. Upon implementation of the compliance schedule we intend to discontinue the instant collection and consolidate the burden estimate into the existing collection as appropriate.

5. Impact on Small Businesses or Other Small Entities

While the regulations provide for no exemptions, there is a 10-year implementation schedule associated with the requirements. FDA assists small businesses in complying with its requirements through Regional Small Business Representatives and through the scientific and administrative staffs within the agency. Also, we provide a Small Business Guide on our website at http://www.fda.gov/ForIndustry/SmallBusinessAssistance/default.htm.

6. Consequences of Collecting the Information Less Frequently

Information collection schedule is consistent with regulatory requirements as mandated by the Federal Food, Drug, and Cosmetic Act.

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 the Federal Register of October 4, 2017 (82 FR 46248), we published a 60-day notice requesting public comment on the proposed extension of this collection of information. Two comments were received in response to the notice, however both comments discussed specific requirements found in FDA regulations rather than the four information collection topics solicited in our notice under the PRA.

9. Explanation of Any Payment or Gift to Respondents

No payments or gifts are provided to respondents of the information collection.

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

We estimate the burden for the information collection as follows:

12a. Annualized Hour Burden Estimate

These FDA regulations describe 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 regulations require, 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. In addition, the regulations require that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential.

In addition, the final rule provided for a 10-year implementation schedule for compliance with the relevant regulations. As the implementation schedule is realized, FDA plans to discontinue this separate information collection and incorporate the provisions into existing collections, as appropriate. The content and format requirements apply to:

- applications submitted on or after June 30, 2015 (§§ 314.50 (21 CFR 314.50), 314.70(b), 601.2 (21 CFR 601.2), and 601.12(f)(1));

- amendments to applications pending on June 30, 2015 (§§ 314.60 (21 CFR 314.60), 601.2, and 601.12(f)(1));

- supplements to applications approved from June 30, 2001 to June 30, 2015 (§§ 314.70(b) and 601.12(f)(1)); and

- 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) and 601.12(f)(3)).

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).

As indicated in Tables 1 and 2, we estimate that the burden associated with the information collection to be 1,598,000 hours.

Table 1. Estimated Annual Reporting Burden[1]

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 6/30/15 (§§ 314.70(b), 601.12(f)(1))	390	26	10,150 (Submitted 3rd, 4th, and 5th years after 6/30/15)	120	1,218,000
Annual report submission of revised labeling for applications that contain a pregnancy category, approved before 6/30/01 (§§ 314.70(d), 601.12(f)(3))	320	~17	5,500 (Submitted 3rd year after 6/30/15)	40	220,000
Total					1,438,000

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

Table 2. Estimated Annual Third-Party Disclosure Burden[1]

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 6/30/15, including amendments to applications pending as of 6/30/15 (§§ 314.50, 314.60, 314.70(b), 601.2, 601.12(f)(1))	390	~10	4,000 (Submitted during 10-year period after 6/30/15)	40	160,000

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

FDA estimates that approximately 4,000 applications containing the subject labeling will be submitted by approximately 390 applicants and repackagers and relabelers to FDA over the 10-year period beginning June 30, 2015. This figure (4,000 applications) includes labeling for approximately 800 applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 505(b)) or section 351 of the Public Health Service Act (42 U.S.C. 262), 1,200 applications submitted under section 505(j) of the FD&C Act, and 2,000 revised drug product labeling from repackagers and relabelers for approximately 2,000 applications. This estimate also includes labeling amendments submitted to FDA for applications pending as of the effective date of the final rule. FDA estimates that it will take applicants approximately 40 hours to prepare and submit the subject labeling. This estimate applies only to the requirements covered by the final rule 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 (21 CFR 201.56), 201.57, and 201.80 is approved by OMB under control numbers 0910-0572 and 0910-0001.

In addition, during the 3rd, 4th, and 5th years after the effective date, we estimate we will receive approximately 10,140 supplements to applications that were either approved from June 30, 2001, to the effective date or were pending as of the effective date. This estimate includes supplements for approximately 1,080 NDAs, BLAs, and efficacy supplements; 1,320 ANDA supplements; and 7,750 drug product labeling supplements from repackagers and relabelers. FDA estimates that approximately 390 application holders, repackagers, and relabelers will submit these supplements, and that it will take approximately 120 hours to prepare and submit each supplement.

We estimate that application holders will submit 5,500 annual reports to FDA during the third year after the effective date for applications that contain a pregnancy category, approved before June 30, 2001. This estimate includes approximately 1,340 NDAs and BLAs, and approximately 4,160 ANDAs containing labeling changes as a result of the final rule. FDA estimates that approximately 320 application holders will submit these annual reports, and that it will take approximately 40 hours for each submission.

12b. Annualized Cost Burden Estimate

As referenced in our final rule, we estimated 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

Costs to the Federal government are absorbed through existing resource allocations for review and action regarding NDAs, ANDAs, BLAs, and any supplemental applications.

15. Explanation for Program Changes or Adjustments

The burden for the information collection remains unchanged; however we note inadvertent calculation errors in our 60- and 30-day notice publications. As discussed in the supporting statement, we plan to discontinue the information collection upon realization of the compliance schedule.

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

Display of OMB Expiration Date is appropriate.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.