SUPPORTING STATEMENT

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (OMB Control Number 0910-0572)

A. Justification

1. Circumstances of Information Collection

FDA's final rule entitled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (the final rule), which published on January 24, 2006 (71 FR 3922), and was effective on June 30, 2006, amended FDA's regulations governing the format and content of labeling for human prescription drug and biological products to require that the labeling of new and recently approved products contain highlights of prescribing information, a table of contents for prescribing information, reordering of certain sections, minor content changes, and minimum graphical requirements. These revisions were intended to make it easier for health care practitioners to access, read, and use information in prescription drug labeling, to enhance the safe and effective use of prescription drug products, and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information.

Section 201.56 (21 CFR 201.56) requires that prescription drug labeling contain certain information in the format specified in either § 201.57 (21 CFR 201.57) or § 201.80 (21 CFR 201.80), depending on when the drug was approved for marketing. Section 201.56(a) sets forth general labeling requirements applicable to all prescription drugs. Section 201.56(b) specifies the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in §§ 201.56(d)

and 201.57. Section 201.56(c) sets forth the schedule for implementing these revised content and format requirements. Section 201.56(e) specifies the sections and subsections, required and optional, for the labeling of older prescription drugs not subject to the revised format and content requirements.

Section 201.57(a) requires that prescription drug labeling for new and more recently approved prescription drug products include "Highlights of Prescribing Information." Highlights provides a concise extract of the most important information required under § 201.57(c) (the Full Prescribing Information (FPI)), as well as certain additional information important to prescribers. Section 201.57(b) requires a table of contents to prescribing information, entitled "Full Prescribing Information: Contents," consisting of a list of each heading and subheading along with its identifying number to facilitate health care practitioners' use of labeling information. Section 201.57(c) specifies the contents of the FPI. Section 201.57(d) mandates the minimum specifications for the format of prescription drug labeling and establishes minimum requirements for key graphic elements such as bold type, bullet points, type size, and spacing.

Older drugs not subject to the revised labeling content and format requirements in § 201.57 remain subject to labeling requirements at § 201.80 (in the final rule, former § 201.57 was redesignated as § 201.80). Section 201.80(f)(2) requires that within 1 year, any FDA-approved patient labeling be referenced in the "Precautions" section of the labeling of older products and either accompany or be reprinted immediately following the labeling.

2. Purpose and Use of Information

The regulations are part of FDA's strategic initiative to manage the risks of medical product use and reduce adverse events involving the products that it regulates. The regulations on the content and format of labeling will make it easier for health care practitioners to access, read, and use information in prescription drug labeling, thereby increasing the extent to which they rely on labeling to obtain information. The regulations reflect those that the agency believes will enhance the safe and effective use of prescription drug products, and in turn, reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. The requirements are important to the success of other initiatives aimed at improving patient care and decreasing the likelihood of medication errors. For example, the DailyMed, a collaboration between FDA and the National Libarary of Medicine will be an innovative means of disseminating up-to-date and comprehensive medication information electronically for use in information systems that support patient care. The DailyMed will make current information about FDA-regulated products readily available to physicians, other health care practitioners, and patients. In addition, prescription drug labeling in the new format may also be utilized with electronic prescribing systems under development.

3. Use of Improved Information Technology

As discussed in this document, the drug product labeling affected by these regulations are submitted to FDA for approval as part of the NDA, ANDA, BLA or a

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 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:

- “Indexing Structured Product Labeling.”
- "Providing Regulatory Submissions in Electronic Format - Content of Labeling."
- "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and related Submissions Using the eCTD Specifications.”
- "Providing Regulatory Submissions in Electronic Format - General Considerations."
- "Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports."
- "Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling."
- "Providing Regulatory Submissions in Electronic Format – Receipt Date."
- "SPL Standard for Content of Labeling Technical Qs and As."

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

4. Efforts to Identify Duplication

The information collection required as a result of these regulations does not duplicate any other information collection.

5. Involvement of Small Entities

Under the Regulatory Flexibility Act, FDA analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements. As discussed in the "Analysis of Impacts" section of the January 24, 2006, final rule, FDA concluded that these regulations would not have a significant impact on most small entities, as defined by the Regulatory Flexibility Act. However, it is possible that a few small firms may be significantly affected.

6. Consequences If Information Collected Less Frequently

The part of a prescription drug product's approved labeling directed to health care practitioners is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals. The primary purpose of prescription drug labeling is to provide practitioners with the essential information they need to prescribe the drug safely and

effectively for the care of patients. This purpose would be hindered without the information collection requirements set forth in the regulations.

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

There is no inconsistency resulting from these regulations.

8. Consultation Outside the Agency

As required under section 3506(c)(2)(B) of the Paperwork Reduction Act, FDA provided an opportunity for public comment on the information collection provisions of these regulations in the September 29, 2008, Federal Register (73 FR 56592). FDA received no comments on the information collection estimates.

9. Remuneration of Respondents

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

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. Estimated Reporting Burden

The PRA information collection analysis in the final rule (71 FR 3964-3967) (currently approved under OMB Control Number 0910-0572) estimated the reporting burden for a multi-year period. We are requesting that OMB extend approval for the information in this collection, as described below, that will continue to be submitted to FDA during this multi-year period.

Annual Burden for Prescription Drug Labeling Design, Testing, and Submitting to FDA for new NDAs and BLAs (§§ 201.56 and 201.57) (Table 1)

New drug product applicants must: (1) Design and create prescription drug labeling containing Highlights, Contents, and FPI, (2) test the designed labeling (e.g., to ensure that the designed labeling fits into carton-enclosed products), and (3) submit it to FDA for approval. Based on the projected data estimated in the final rule, FDA estimates that it takes applicants approximately 3,349 hours to design, test, and submit prescription drug labeling to FDA as part of an NDA or BLA under the revised regulations. Approximately 85 applicants submit approximately 107 new applications (NDAs and BLAs) to FDA per year, totaling 358,343 hours.

Burden Associated with Labeling Supplements for Applications Approved Within 5 Years Prior to the Effective Date of the Rule (§ 201.57) (Table 2)

The final rule required that prescription drug applications approved during the 5 years before, or pending on, the effective date conform to format and content requirements at § 201.57. For these products, applicants must redesign and negotiate the

labeling, including Highlights and Contents, test the redesigned labeling, and prepare and submit that labeling to FDA for approval. Based on the projected data estimated in the final rule, labeling supplements for a total of approximately 344 innovator products are expected to be submitted to FDA over a 5-year period (beginning in year 3 and ending in year 7 after the effective date of the final rule). Approximately 172 applicants submit these labeling supplements, and the time required for redesigning, testing, and submitting the labeling to FDA is approximately 196 hours per application, totaling 67,424 hours.

Burden Associated with Revised Labeling Efficacy Supplements Submitted on or After the Effective Date of the Rule (§§ 201.56(d) and 201.57) (Table 2)

Efficacy supplemental applications for older drugs submitted to FDA on or after the effective date of the final rule are subject to the content and format requirements of §§ 201.56(d) and 201.57. To meet these requirements, applicants must revise the existing labeling for these products. Each year an increasing number of innovator drug labeling will have been revised, and over time, very few efficacy supplements independently will generate labeling revisions. Based on the projected data estimated in the final rule, the number of affected efficacy supplements over 10 years, beginning with year 3, is 186, with a decreasing number each year over the period. Approximately 172 applicants will trigger approximately 186 efficacy supplements, each one requiring approximately 196 hours to revise the labeling in the application, totaling 36,456 hours. (As stated in the final rule, in addition to this burden, a minimal annual reporting burden (fewer than 7) will continue indefinitely).

Burden Associated with Revised Labeling for Efficacy Supplements for Generic Drug Products (§ 201.57) (Table 2)

Based on the projected data estimated in the final rule, beginning in year 3 and continuing throughout the 10-year period analyzed, approximately 42 generic applicants per year must submit labeling supplements. Approximately 336 already approved generic drug applications must submit labeling supplements over the 10-year period after the effective date of the rule. The time required to revise and submit this labeling to FDA is approximately 27 hours per application, totaling 9,072 hours. (As stated in the final rule, in addition to this burden, a minimal annual reporting burden associated with a very small number of generic applications referencing older drugs may continue indefinitely).

C. Capital Costs

As discussed in the final rule, a small number of carton-enclosed products may require new packaging to accommodate longer inserts. As many as 5 percent of the existing products affected by the final rule (i.e., products with new efficacy supplements, products approved in the 5 years prior to the effective date of the rule, and affected ANDAs) may require equipment changes at an estimated cost of $200,000 each product.

Table 1. – Estimated Reporting Burden For New Drug Applications

Category (21 CFR section)	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Annual Burden for Labeling Requirements in §§ 201.56 and 201.57	85	1.26	107	3,349	358,343
TOTAL:					**358,343**

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

TABLE 2. – ESTIMATED REPORTING BURDENS FOR LABELING REVISIONS TO ALREADY-APPROVED DRUG PRODUCTS

Category (21 CFR section)	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Burden associated with revised labeling for applications approved within 5 years prior to June 30, 2006 (§ 201.57)	172	2	344	196	67,424
Burden associated with					

revised labeling for efficacy supplements submitted on or after June 30, 2006 (§§ 201.56(d) and 201.57)	172	1.08	186	196	36,456
Burden associated with revised labeling for efficacy supplements for generic drug products (§ 201.57)	42	8	336 (for years 1-10)	27	9,072
TOTAL:					**112,952**

There are no operating and maintenance costs associated with this collection of information.

13. Estimates of Total 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 the regulations. Using the averaged wage rate of $50.00 per hour, and multiplied times the annual burden hours estimated in the tables above, the total cost burden to respondents is $23,564,750 (471,295 hours x $50).

14. Estimates of Annualized Cost Burden to the Government

Using the estimate of $50.00 per hour as the hourly wage for FDA reviewers to review labeling submissions under the proposal, and estimating that it takes an average of approximately 40 hours to review each of the estimated 973 submissions, the annualized cost to FDA as a result of this proposed rulemaking would be $1,946,000 (40 hours x 973 submissions x $50).

15. Changes In Burden

The changes in burden from the information collection in the final rule are the result of reductions in the number of submissions that have occurred because 3 years have expired under the implementation plan.

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 - 0572

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 on Content and Format of Labeling for Human Prescription Drug and Biological Products

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

9. Keywords: prescription drug labeling, FDA-approved patient labeling

10. Abstract. FDA regulations governing the format and content of labeling for human prescription drug and biological products requiring that the labeling of new and recently approved products contain highlights of prescribing information, a table of contents for prescribing information, reordering of certain sections, minor content changes, and minimum graphical requirements.

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. Total Reporting burden

a. Number of respondents 172

b. Total responses 973

1. Percentage of these responses collected electronically approximately 75 %

c. Total hours requested 471,295

d. Current OMB inventory 496,383

e. Difference

f. Explanation of difference

1. Program change change in number of submissions

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. [ ] 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: Elizabeth Berbakos

	Phone: _____