Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products - Proposed Rule

RIN: 0910-AG18

SUPPORTING STATEMENT

A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is proposing to amend its labeling regulations to require electronic distribution of prescribing information for human prescription drugs. This is intended to facilitate the distribution of updated prescribing information as new information becomes available and as changes in prescribing information are made. FDA is taking this action so that the most current prescribing information for distributed prescription drugs will be available and readily accessible to healthcare professionals at the time of clinical decision-making and dispensing. This proposed rule complements other FDA and Department of Health and Human Services initiatives that are intended to provide accessible electronic drug product information to healthcare professionals, consumers, and/or the public. These initiatives include the electronic prescribing provisions of the Medicare Prescription Drug Improvement and Modernization Act, the requirement for bar codes on certain drug product labels, the requirement for submission of electronic labeling in product approval applications and electronic registration of drug establishments and listing of drug products.

Currently, prescribing information that accompanies human prescription drugs is provided in paper form. The paper form of the prescribing information is either attached to the immediate container or it may accompany the product if the product has an outside container or package. It is possible that the paper form of the prescribing information accompanying a product in interstate commerce or in the possession of a pharmacist or other healthcare professional may not contain the most current information because, as described in further detail below, the paper form accompanying the product may have been printed and distributed prior to more recent labeling changes.

The manufacturer of a prescription drug may take several weeks to months to incorporate a labeling change for the product and print new paper forms of the updated prescribing information. This process includes printing, folding, storing until used, and attaching the prescribing information to the immediate container or placing the prescribing information within the outer package that may house the product. Each of these steps typically requires equipment made specifically for these functions. For some products, manufacturers may only produce updated printed prescribing information once a year. In cases such as this, the information in the paper form of the prescribing information may be out-dated if the product is not manufactured frequently, and there have been new labeling changes since manufacturing. Because of these factors, products with prior versions of the prescribing information in paper form may remain in use. Based on a review of supplements to applications reflecting a labeling change submitted to FDA over a three year period, we estimate a firm may submit an average of three labeling changes per year for various reasons.

Electronic forms of the prescribing information for many, but not all, human prescription drugs, are currently available through various sources to health professionals and consumers in a variety of formats. This information, though, may not be the most up-to-date version of the prescribing information. The proposed rule would require that the drug's most current labeling be electronically submitted to FDA in a format that FDA can process, review, and archive each time the labeling content is changed. FDA will use these submissions to populate the publicly-available labeling repository so that the updated labeling is available in a timely fashion to prescribers, pharmacists, and healthcare providers. This proposed rule would require the manufacturer to verify that its product labeling appears on the FDA's labeling repository website and is accurate, complete and up-to-date within two business days of its posting, and to notify FDA within two business days of posting if the labeling on the FDA's labeling repository website is not accurate, complete and up-to-date. Since FDA's labeling repository website will link prescribing information to specific National Drug Codes (NDCs), the prescribing information will be product specific and will correspond to the NDC that may appear on a product's label. The agency expects that the repository will also be searchable by, among other things, active

ingredient and proprietary name. In this way, FDA will be able to provide the public with a complete source for the most current prescribing information for products approved under NDA's, ANDA's, BLA's, and those marketed and not approved.

Post-approval, safety-related labeling changes to the prescribing information that may impact public health include adding or strengthening a contraindication, warning, precaution, or adverse reaction, or the addition of, or changes to, a boxed warning for the product. During an internal review of labeling changes made for new molecular entities, there were 36 new boxed warnings issued from 2005 to 2007 (calendar years). It should be noted that approximately two-thirds of these boxed warnings were the result of class-related safety labeling changes that added new boxed warnings to several different products in specific drug classes, including antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), and atypical antipsychotics. Our regulations require that the boxed warning information be explained in more detail in the "Contraindications" or "Warnings and Precautions" sections of the labeling (21 CFR 201.57(c)(1)). Therefore, changes to different sections of the prescribing information associated with the new boxed warning may be submitted to the Agency in one supplemental application. Due to the serious risk associated with the product and to promote optimal patient care, boxed warnings and additional warnings and precautions information should be available to the healthcare professional as soon as possible from a reliable and consistent source.

The proposed rule would not affect the applicant's responsibilities regarding the content of labeling or the process for submitting labeling changes to FDA for approval. The prescribing information component of labeling would contain the most current changes approved by FDA, changes being effected, and editorial changes that may be submitted in the annual report.

This proposed rule would require submission of the prescribing information, in a format that FDA can review, process, and archive for posting on the FDA's labeling repository website. In addition, the manufacturer would be required to provide a release date, on which the labeling will be posted on the FDA labeling repository. Generally, it is expected that labeling can be posted as early as the next business day following its submission. Upon approval of a new drug, the labeling must be

submitted in time to be posted on FDA's labeling repository before the product enters interstate commerce. In the case of a labeling change, the regulation will require manufacturers who are NDA, ANDA and BLA application holders to submit the labeling within two business days, following FDA approval of a prior approval supplement. Other manufacturers, such as repackagers and relabelers will be required to submit labeling two business days following the posting of the application holder's updated labeling. The labeling should be submitted to FDA for posting on the same day that a CBE supplement is submitted to the Agency. In addition, the manufacturer would use the version of the prescribing information incorporating the change when it receives a request from a healthcare provider to fax, email, or mail the prescribing information. Minor changes to the prescribing information that would normally be documented in the applicant's annual report to the FDA would still be reported and described in the annual report, but the prescribing information reflecting the labeling update would be sent to FDA at the time of the change for posting on FDA's labeling repository website. Applicants would ensure that pending supplements are amended to reflect all recent approved labeling changes so that the most current labeling is used for consideration of the pending supplement (submissions in SPL format include version control capabilities to make certain that the most current labeling is submitted.). This will help to ensure that the most current labeling is considered by FDA and available to the public.

2. Purpose and Use of the Information Collection

This rulemaking is intended to facilitate the distribution of updated prescribing information as new information becomes available and as changes in prescribing information are made. FDA is taking this action so that the most current prescribing information for distributed prescription drugs will be available and readily accessible to healthcare professionals at the time of clinical decision-making and dispensing.

3. Use of Improved Information Technology and Burden Reduction

On December 11, 2003, FDA amended the regulations governing the format in which certain labeling is required to be submitted for review with NDAs, ANDAs, certain BLAs, supplements, and annual reports (68 FR 69009). The final rule required the electronic submission of certain prescribing information in a form that FDA can process, review, and archive. This action was taken to simplify the prescribing information review process and to provide more timely approval of prescribing information changes. To support this requirement, we issued guidance in April 2005 titled, "Providing Regulatory Submissions in Electronic Format – Content of Labeling." This guidance describes the SPL standard, which is based on extensible markup language (XML), as the most up-to-date electronic format that FDA can use to process, review, and archive prescribing information and other labeling changes that are submitted electronically as part of a regulatory submission.

In 2007, Congress enacted the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA). Section 224 of FDAAA, which amends section 510(p) of the FD&C Act (21 U.S.C. 360(p)), expressly requires owners and operators of establishments engaged in the manufacture of drugs (manufacturers) to electronically submit drug establishment registration and drug listing information unless a waiver is granted. As part of the drug listing information, each manufacturer must submit a copy of all components of each drug's current labeling to the Agency with the exception of promotional labeling (21 CFR 207.25(b)). To assist manufacturers with electronic submissions of drug establishment registration and drug listing information, FDA issued a guidance on May 28, 2009 titled, "Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing." This guidance provides recommendations to manufacturers on how to create and submit separate electronic SPL files containing drug establishment registration and drug listing information, including a copy of the required components of labeling, for each marketed prescription human drug, including biological products covered by 21 CFR Part 207. The FD&C Act currently requires manufacturers to update the drug listing information (which includes the product labeling) at least twice a year, once in June and once in December (21 U.S.C. 360(j)(2)).

The proposed rule also complements other FDA initiatives that are intended to provide accessible electronic drug product information to healthcare professionals, consumers, and/or the public. These initiatives include the electronic prescribing provisions of the Medicare Prescription Drug Improvement and Modernization Act and the requirement for bar codes on certain drug product labels.

To improve the use of information technology in the submission of marketing applications for human drugs and related reports, FDA has developed and issued guidances for industry on electronic submissions. These guidance documents are available on FDA's Web site at http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

4. Efforts to Identify Duplication and Use of Similar Information

This rulemaking does not duplicate other FDA initiatives.

5. Impact on Small Businesses or Other Small Entities

This impact is discussed in the "Analysis of Impacts" section of the proposed rule:

> We used data from the U.S. Census Bureau to determine the percent of small businesses that would be affected by the proposed rule. The Census collects detailed data by employment size and sales on an establishment basis for the Economic Census. Because Census data are collected by establishment rather than by firm, the percentage of firms that would be considered small is overstated Table 21 of the proposed rule, but it is clear that with the exception of hospitals and supercenters that most of the firms affected would be considered small. Table 21 of the proposed rule shows that the proposal would affect a substantial number of small entities.

Prescribing information providers (excluding blood manufacturers) would realize net savings from the proposed rule, but the impact would vary greatly by the number of products and SKUs a firm produces and the volume of prescribing information that each firm prints annually. Small entities in these sectors would benefit, but the greater the numbers of products and sales, the greater would be the one-time costs and the annual savings.

The costs of the proposed rule would fall on potential users of the prescribing information. These costs, as described in detail in previous sections and summarized in tables 12 through 17 of the proposed rule, include additional hardware, training, Internet access, printing, and access and printing time. Table 17 of the proposed rule shows the average costs per user establishment; most of the affected establishments are small entities (see Table 21 of the proposed rule). The costs could be over $1,000 per establishment for small pharmacies and almost $2,700 per establishment for hospital users. These costs would vary by an establishment's sales volume because there would presumably be greater numbers of prescriptions written and dispensed. Individual healthcare professionals' overall experience and comfort with electronic media would also influence the cost per establishment of this proposed rule.

Manufacturers of blood and blood component products, most of which are small entities, would also incur a net cost as a result of the proposed rule. Unlike pharmaceutical drug products, the prescribing information for blood and blood component products does not have to accompany every container in a shipment; it would take many years before the accumulated

savings from no longer providing the prescribing information in paper form surpassed the one-time cost to change all the container labels.

There is little difference in costs of delaying the implementation of the rule for users of the prescribing information. It would also not be feasible to operate a dual system allowing some users to continue receiving the paper form of the prescribing information for a longer period of time. Finally, because most users are small entities, exempting or delaying the proposed rule for small entities would in effect negate the proposed rule.

6. Consequences of Collecting the Information Less Frequently

This rulemaking does not amend the frequency that the required prescribing information must be provided.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances that would result from the proposal, other than those covered by OMB's approval for 0910-0001 and 0910-0338.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In the FEDERAL REGISTER of April 2, 2007, FDA announced a public hearing to "solicit views and information from interested parties concerning the concept of electronic distribution of FDA-approved prescribing information currently contained in the package insert * * * for human prescription drug and biological products" (72 FR 15701). FDA also sought information "on the feasibility of establishing a modern and efficient process for industry to electronically distribute prescribing information to dispensers" and asked specific questions to evaluate the possible benefits of electronic prescribing information and the logistics of such an electronic system (72 FR 15701 and 15702). At the public hearing, FDA explained that it is committed to facilitating the transition to use of electronic information and capitalizing on the efficiencies that an electronic environment could offer. The public hearing and comments submitted to FDA in connection with the public hearing suggested that:

- The majority believe that electronic distribution of prescribing information would give healthcare professionals access to the most current information in the labeling, and this would result in better care for patients and improved public health.
- Electronic distribution of prescribing information would be better for the environment (because most prescribing information provided in paper form is discarded) and could be more user-friendly if individuals are able to manipulate font sizes to make the print larger and easier to read.
- Use of electronic distribution of prescribing information should not impose undue hardship on pharmacists and pharmacies in regard to workflow, process, and costs related to implementing a new system (which may include training, maintenance, and printing).
- Education or training should be provided to healthcare professionals if we convert to electronic distribution of prescribing information.
- There are varying opinions as to whether we should require electronic distribution of prescribing information for all prescription drugs, whether there should be a transition period whereby paper forms would co-exist with the electronic format, and whether certain drugs, due to warnings for the drugs or special instructions regarding their use, always should be accompanied by prescribing information in paper form.
- Parties also differed as to whether we should provide for other sources of prescribing information if emergency situations resulting in a loss of electricity or Internet access arose. Some suggested that we should create an annual compendium that healthcare professionals could consult as a back-up resource.

FDA considered these comments in drafting this proposed rule. For example, the agency agree that electronic distribution of prescribing information should give health professionals access to the latest information for a particular human prescription drug (including covered biological products) and contribute to improving patient care. Patients would also have access to up to date electronic prescribing information from FDA's labeling repository website. Since patient labeling is not subject to this rule, warnings, risk information and special instructions for use in patient labeling will continue to be provided in paper form to patients. FDA also agree that electronic distribution of prescribing information may reduce waste, although it did not evaluate the environmental impacts resulting from fewer paper forms of labeling and did not cite environmental benefits as a justification for this proposed rule.

This proposal represents a continuation of agency efforts to improve access to prescription drug labeling and to make a transition to electronic distribution of prescribing information. The proposed rule invites additional comments on the use of prescribing information by prescribers and other healthcare professionals as well as consumers/patients.

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (PRA), FDA provided an opportunity for public comments on the information collection requirements of the proposed rule that published in the FEDERAL REGISTER of 12/18/2014 (79 FR 75506).

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of information received by FDA under the rulemaking is consistent with the Freedom of Information Act, FDA's regulations under 21 CFR Part 20, and 21 CFR 314.430.

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this information collection.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

The proposed rule would amend certain labeling regulations to require applicants or manufacturers of human prescription drugs (including biological products and blood and blood components intended for transfusion) to distribute the prescribing information for these drugs electronically. This information is currently distributed in paper form on or within the package from which a prescription drug is dispensed. The electronic distribution requirements of this regulation would not apply to patient labeling (including patient package inserts and Medication Guides), which would continue to be provided in paper form, as currently required by applicable regulations. The proposed regulation would require manufacturers and applicants to submit labeling containing prescribing information to FDA for distribution via FDA's labeling repository Web site every time there is a change in the labeling and to review the labeling posted at FDA's Web site to ensure that the correct version of the labeling appears in the repository. The regulation would require a product's immediate container label or a label affixed to the immediate container by other means, such as a peel-back label (if the immediate container label is too small to bear the statement) and outside package to bear a statement directing health care professionals to FDA's labeling repository to view the electronic version of prescribing information and to provide a toll-free telephone number maintained by the manufacturer to receive requests that the manufacturer send an emailed, faxed, or mailed paper copy of the prescribing information. The prescribing information would be distributed in paper form where a pharmacist or health care provider requests that the manufacturer send a paper copy of the labeling or where an exemption to the electronic distribution of labeling requirements has been granted. Manufacturers and applicants of exempted products would distribute prescribing information in paper form on or within the package from which the product is dispensed and would not be required to distribute the labeling electronically or by FAX, email, or mail. We are taking this action to help ensure that the most current prescribing information is publicly accessible for the safe and effective use of the product.

A. Summary of Provisions in Proposed Rule That Contain Collections of Information

1. Labeling Accompanying a Product To Include Electronic Distribution of Prescribing Information (proposed §§ 201.100(c)(1), (c)(3), (c)(4), (c)(5), (d), and (d)(2); 201.306; 201.310; 606.122; 610.61(k) and (n)).

This proposed rule would require that prescribing information be distributed through electronic means, unless FDA exempts a specific product from the electronic distribution requirement or unless the manufacturer is requested to send a paper copy of the labeling. The addition of new § 201.100(c)(3) would require prescribing information to be distributed electronically and, with the exceptions noted in this document, not in paper form. The mechanism by which the labeling will be distributed electronically would be through posting on the FDA labeling repository at *labels.fda.gov*. The labeling repository would be initially populated with labeling that had already been electronically submitted to FDA to comply with current requirements (part 207, and §§ 314.50(l), 314.94(d), 601.14). On the effective date of this regulation, manufacturers and applicants would not need to make a new submission of labeling to FDA under this regulation if the labeling available in the repository is current. However, before distributing product with labels directing users to *labels.fda.gov* for prescribing information, the manufacturer or applicant must review the prescribing information in the repository, and, if the prescribing information in the repository is not current, must submit the current version of the prescribing information.

This proposed rule would revise § 201.100, with the addition of paragraph (c)(4), which would require that, upon initial approval of a drug, or following any change to approved labeling, the applicant or other manufacturer must submit the content of labeling in an electronic format to FDA at the time of the change for distribution via the FDA's labeling repository Web site. Minor changes to the prescribing information would continue to be reported in the applicant's annual report; however, the revised labeling would be required to be submitted to FDA at the time of the change for distribution via FDA's labeling repository Web site. Submissions at the time of a change would ensure that the most up-to-date prescribing information is posted on the FDA's labeling repository Web site and available to the public, particularly health care professionals, for use with the drug at the time it is prescribed, dispensed, or administered.

2. Label Statement for Human Prescription Drugs, Including Biological Products and Blood and Blood Components Intended for Transfusion, on the Product's Immediate Container Label and Outside Package (Proposed §§ 201.100(b)(8), 606.121(c), 610.60(a)(8), and 610.61(t)).

Current §§ 201.100(b), 606.121, 610.60, and 610.61 set forth the information that is required to appear on the label of the prescription drug product or the container label and outside package of biological products. This proposed rule would require, except where an exemption is granted, that all immediate container labels and outside packages bear a statement directing users to the FDA labeling repository to obtain the current prescribing information or circular of information and to a toll-free number to request that this information instead be provided by mail, email, or FAX. In order to ensure that the statement is readable, this statement would be no smaller than 6-point type. Where the immediate container label does not have sufficient space to bear this statement, it would be required to be affixed to the immediate container by other means, such as a peel-back label.

3. Provision of Prescribing Information via Fax, Email, or Mail (Proposed § 201.100(c)(5)) and Exemptions (§ 201.100(g)).

To ensure that the prescribing information is readily accessible if Internet access is not available to the health care professional seeking the current prescribing information, the label statement would be required to include a toll-free telephone number on the product's immediate container label and outside package. The health care professional would call this number to request the most current prescribing information by FAX, email, or mail. The manufacturer would be responsible for ensuring that the toll-free telephone number is current, fully functioning, and maintained so that there is always an alternate method available (24 hours a day, 7 days a week) to obtain the current prescribing information if the requestor cannot access the information electronically. The manufacturer would be responsible for taking adequate steps to ensure that it promptly provides the prescribing information to the requestor.

Proposed § 201.100(g) would permit a manufacturer to request that a drug or biological product be exempt from the requirements for electronic distribution of labeling set forth in this section. The exemption request must document why compliance with the electronic distribution of labeling requirements could adversely affect the safety, effectiveness, purity, or potency of the drug; is not technologically feasible; or is otherwise inappropriate and must document that the concerns underlying

the request could not reasonably be addressed by other measures. In addition, FDA would be able to exempt products on its own initiative. Manufacturers and applicants of exempted products would be required to distribute prescribing information in paper form on or within the package from which the drug is to be dispensed.

B. Estimates of Reporting Burden

1. Electronic Submissions of Prescribing Information to the Agency, for Inclusion in the Electronic Labeling Repository (Proposed § 201.100(c)(4)).

Prescribing information for prescription drugs (*i.e.*, content of labeling required under § 201.100(d)) already must be submitted to the Agency in an electronic format that the Agency can process, review, and archive as part of NDAs, ANDAs, BLAs, and annual reports. (See §§ 314.50(l), 314.94(d), 601.14(b), and 314.81(b).) These submissions are approved by OMB under the PRA under OMB control numbers 0910-0530 and 0910-0338. In addition, under section 510(p) of the FD&C Act, enacted in 2007, listing information required to be submitted under section 510(j) of the FD&C Act and implementing regulations in part 207 has been required to be submitted electronically since June 2009. Labeling for all drugs is a subset of that information, including prescribing information both for prescription drugs that are subject to approved NDAs, ANDAs, and BLAs, and for prescription drugs that are not subject to approved applications. Information collections associated with the electronic submission of listing information are approved under OMB control number 0910-0045. In May 2009, FDA issued a guidance entitled "Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing," (*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf*. In this guidance, FDA explained that labeling updates to applications under the content of labeling regulations could be duplicative in content and format of labeling required to be submitted for listing under part 207. To avoid duplicative submissions, FDA recommended that applicants simultaneously fulfill the "content of labeling" and listing requirements regarding submission of labeling by submitting a single SPL file through the listing system and cross-referencing it in their applications.

FDA intends to adopt the same electronic format used in these other submissions (currently SPL) for submitting labeling required under this proposed regulation. FDA intends to use labeling previously submitted under these other provisions to initially populate the labeling repository prior to the effective date of the rule, so that where labeling is current, no new submissions will be needed to achieve initial compliance. Further, if this proposed rule becomes final, going forward, a single submission will in many cases fulfill the requirements under this regulation, under the content of labeling requirements in parts 314 and 601, and under certain provisions of part 207. Because this regulation would require submission of labeling in electronic form prior to the time at which such labeling must be submitted under those other provisions (and therefore, may result in some additional submissions not accounted for in those information collections), in the burden estimates that follow, FDA has included the estimated burden of all submissions that would be required to meet the terms of this proposed regulation, without excluding those that would duplicate submissions already addressed under one of the previously named provisions. In the future, however, FDA anticipates that if this rule becomes final and its information collection provisions are approved, it would be appropriate to reduce the estimated information collection burdens approved under control numbers 0910-0530, 0910-0338, and 0910-0045, as FDA does not intend to require duplicative submissions.

To estimate the burden hours per submission, we adopted an estimate of 1.25 hours per submission (which was the time estimate used for submission of electronic content of labeling under the most recent OMB extension of approval for that information collection, approved under OMB control number 0910-0338). The total estimated number of labeling submissions is the sum of several items.

The proposed regulation would require applicants to submit the labeling upon initial approval of a drug. To estimate the annual number of submissions for newly approved products, the Agency reviewed the number of NDA and ANDA approvals and new licenses for biological products to estimate the average number of approvals on an annual basis. We have estimated that there will be approximately 106 NDA applicants who had an average of 150 NDA approvals per year and approximately 250 ANDA applicants who had 1,200 ANDA approvals. We further estimate that approximately 25

respondents will have an average of 45 BLAs licensed on an annual basis. The total burden hour estimate for these submissions to the Agency is 1,744 hours (1,395 × 1.25 = 1,744).

To estimate the number of labeling submissions that may occur due to updates to the labeling of currently marketed drugs for changes that would require a supplement to an application, we reviewed the number of supplements to NDAs and BLAs reflecting labeling changes that were submitted to FDA in fiscal year 2013 for drug and biological product manufacturers and applicants. An average of 200 applicants submitted an average of 5.5 supplements reflecting labeling changes per applicant per year to the Agency (n = 1,100). The burden hour estimate for these submissions to the Agency is 1,375 hours ([200 × 5.5] × 1.25 = 1,375).

Because this proposed rule would require that applicants submit labeling changes to FDA at the time of the change, there may be submissions to the Agency due to a minor labeling change that previously would have been submitted to the Agency with annual reports (§§ 314.81 and 601.12). To estimate the number of submissions for minor label changes, we assumed that the percentage of firms making label changes via annual reports would be similar to the percentage making changes via supplements and moderate changes being effected in 30 days. Thus, we assumed that one change per applicant, (200 NDA/BLA firms, 225 ANDA firms, and 457 repackagers), for a total of 882 submissions. The total burden hour estimate for these submissions to the Agency is 1,103 hours (882 × 1.25 = 1,103).

Holders of ANDA applications would also submit updated labeling if the applicant who holds the NDA for the innovator drug makes a change to its labeling. We estimate that, on an annual basis, 225 ANDA applicants will make 1,830 submissions of updated labeling. The total burden hour estimate for these additional submissions to the Agency is 2,288 hours (1,830 × 1.25 = 2,288).

This regulation also would require repackagers and relabelers (who are subject to part 207 but not to parts 314 or 612) to submit labeling for their repackaged or relabeled products. Thus, each time an applicant submits updated labeling for a particular product for distribution via the repository, any manufacturers who repack or relabel that product would also be required to submit updated labeling for

posting in the labeling repository. Based on the number of repackers and relabelers that would be subject to this proposal, we estimate that 169 repackers and relabelers would make approximately 566 submissions of updated labeling for NDA products for posting in the labeling repository. In addition, we estimate that 575 repackers and relabelers would make a total of 2,196 submissions of labeling due to an ANDA change. The total burden hour estimate for these submissions to the Agency is 3,453 hours (2,762 × 1.25 = 3,453).

To estimate the annual burden on blood establishments of submitting updated versions of the circular of information and reviewing the posted circular of information, we have estimated that there are 1,300 blood establishments that will be affected by this regulation. The vast majority of blood establishments use the same circular of information, and we estimate that the circular of information will change once annually. Thus, the annual burden of submitting the circular of information is estimated to be 1,625 hours (1,300 × 1.25 = 1,625).

The sums of all of these prior estimates are included in tables 1 and 2 as our estimates of the information collection burden associated with proposed § 201.100(c)(4). In developing our estimates for NDA, ANDA, and BLA products, we are not able to fully account for the possible overlap in respondents submitting labeling under each of the scenarios described in this document. For example, it is possible that a firm submitting labeling in conjunction with a new drug approval might also submit labeling to address a minor labeling change that is reportable in an annual report. In the number of respondents reported in the table, we have not attempted to account for this overlap, but have merely added the number of respondents from each subestimate. The result may be an overestimate of the number of respondents, and a consequent underestimate of the average number of responses per respondent. We invite comment on this and other aspects of our estimate.

2. Submission and Review of Circular of Information by Blood Establishments

Because FDA regulations do not currently require blood establishments to submit the circular of information electronically, blood establishments would be required to submit the circular of information to FDA prior to the effective date of this regulation. To estimate the burden on blood establishments of

submitting updated versions of the circular of information, we have estimated that there are 1,300 blood establishments that will be affected by this regulation. The vast majority of blood establishments use the same circular of information. Thus, the initial burden of submitting the circular of information is estimated to be 1,625 hours (1,300 × 1.25 = 1,625) (table 2).

3. Review of Accuracy and Completeness of Posted Prescribing Information (Proposed § 201.100(c)(4))

Because the labeling repository will be populated with labeling received by the Agency under current requirements, we do not expect a mass submission of prescribing information upon the effective date of this regulation. We require that manufacturers and applicants will verify the accuracy and completeness of the labeling already posted in the repository. This will ensure that labeling available via the FDA labeling repository is accurate and up-to-date. An estimate of establishments that would be affected by this rule was made based on information available in FDA's establishment and product listing databases for drug and biological products. An average of the estimated 1,500 to 2,000 drug manufacturers and applicants was combined with an estimate of 1,800 biological establishments (either licensed establishment or registered blood establishments) for an estimate of 3,550 possible respondents (1,750 + 1,800 = 3,550) for estimating the burden. Collectively, these respondents are responsible for producing 46,000 to 57,600 prescription drug products. An average of this range was used for determining the frequency of responses, resulting in 51,800 individual prescription drug products. The frequency of responses was determined by taking the number of individual prescription drug products divided by the number of respondents, resulting in an estimate of 14.60 responses per respondent. (51,800/3,550 = 14.60).

To estimate the burden hours associated with each submission, we adopted an estimate of 5 hours, which is equal to the time estimated for proofreading the electronic document in the electronic submission final rule (68 FR 69009). We believed this estimate would be similar to the estimate of the amount of time needed to review the accuracy and completeness of the posted prescribing information and compare it with the electronic file that was submitted to the Agency. Although a manufacturer may have to review the accuracy of more than one copy of a single version of the prescribing information

that corresponds to multiple NDC numbers, we believe the 5-hour estimate is reasonable. We request comment on whether this estimate would be applicable to the proposed requirement for reviewing the accuracy and completeness of the prescribing information after it is posted. The total first year burden hour estimate for review for accuracy and completeness of the posted prescribing information is 259,150 hours (3,550 × 14.60 × 5 = 259,150) (table 2). This burden hour estimate includes the time for each manufacturer to review the accuracy and completeness of the prescribing information once it is posted, following a change to the labeling, on the FDA's labeling repository Web site.

In addition, on an annual basis, upon approval of a new NDA, ANDA, or BLA, or upon a change made to prescribing information, all manufacturers and applicants, including repackers of such products will be required to review for accuracy the newly posted prescribing information. As explained in this document, on an annual basis we estimate that there will be 1,395 labeling submissions for newly approved or licensed products (NDAs, BLAs, ANDAs), 1,100 labeling submissions for NDA/BLA supplements, 1,830 labeling submissions for ANDA supplements due to innovators' labeling changes, 882 labeling submissions for annual reportable changes, and 2,762 labeling submissions by repackers due to changes in NDA/ANDA holders' labeling. The total annual burden hour estimate for review for accuracy and completeness of the posted prescribing information for these products is 13,480 hours ([1,395 + 1,100 + 1,830 + 882 + 2,762 = 7,969] × 5 = 39,845) (table 1). The annual burden of checking the circular of information for accuracy is estimated to be 6,500 (1,300 × 5 = 6,500). The total annual burden for drugs, biologics, and blood and blood components is 46,345 hours (table 1).

4. Production of New Product Labels for the Immediate Container Label and Outer Container or Package To Bear Label Statement (Proposed § 201.100(b)(8))

Under proposed § 201.100(b)(8), a new label statement would be required on a product's immediate container label (or on a label affixed to the container by other means, such as a peel-back label, if the immediate container is too small to bear the statement) and outer container or package. A portion of this statement, directing users to access *labels.fda.gov* to view electronic prescribing information, is information provided by FDA to manufacturers and applicants for disclosure to the public, and therefore does not constitute a collection of information under 5 CFR 1320.3(c)(2).

However, the portion of the statement that provides a toll-free number for requesting prescribing information by mail, email, or FAX is not provided by FDA. Accordingly, we have accounted for the burden of including that statement. The frequency of responses was determined by taking the average of the estimated number of stock keeping units (SKUs) (150,000-200,000), divided by the number of respondents, resulting in an estimate of 49.3 responses per respondent (175,000/3,550 = 49.3). To estimate the burden hours associated with adding the statement to existing product labels, we adopted an estimate of 24 hours, which was the estimate used for redesigning labels to incorporate bar codes (see 69 FR 9119 at 9149; February 26, 2004). The total burden hour estimate for adding the new label statement to all presently marketed prescription drugs is 4,200,360 hours (3,550 × 49.3 × 24 = 4,200,360) (table 3).

5. Exemptions (Proposed § 201.100(g))

Under proposed § 201.100(g), the Agency would permit a manufacturer who markets a product to submit a written request to FDA for exemption of a human prescription drug, including a biological product, from the requirements for electronic distribution of prescribing information. We anticipate very few exemption requests will be submitted. Therefore, we estimate that approximately 10 manufacturers and applicants would request an exemption annually, and that each request would take approximately 1 hour to prepare and submit to FDA. In those instances where we grant an exemption, the covered prescribing information would be distributed in paper form by the manufacturer.

Description of Respondents: Persons and businesses, including small businesses and manufacturers responsible for the labeling of prescription drugs, including applicants, repackagers, relabelers, and persons responsible for the labeling of unapproved drugs.

The total estimated annual reporting burden for this collection of information is as follows:

Table 1.--Estimated Annual Reporting Burden[1,2]

Type of Reporting and 21 CFR Section	No. of Respondents	No of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Submission of updated labeling and circular of information under	3,732	2.5	9,269	1.25	11,586

Type of Disclosure and 21 CFR Section	No. of Respondents	Frequency per Disclosure	Total Disclosures	Hours per Disclosure	Total Hours
§ 201.100(c)(4)					
Review of newly labeled statement and immediate container label information outside package (§ 201.100(c)(4))	3,730	42.3	179,069	24	4,297,650
Requests for exemptions under §§ 201.100(d) and 201.100(g)	10	1	10	1	10
Requests to receive prescribing information by fax, e-mail, or mail when requested (§§ 201.100(c)(5) and 201.100(g))	129,090	1	129,090	0.25 (15 minutes)	516,360
Total					574,301

[1]Totals may not sum because frequency numbers are rounded.

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

Table 2.--Estimated One-Time Reporting Burden [1]

Type of Reporting and 21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total One-Time Responses	Average Burden per Response	Total Hours
Review for accuracy and completeness of posted prescribing information under § 201.100(c)(4)	3,550	14.60	51,830	5	259,150
Submission of circular of information by blood establishments under § 201.100(c)(4)	1,300	1	1,300	1.25	1,625
Total					260,775

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

Table 3.--Estimated One-Time Third-Party Disclosure Burden [1]

Table 4.—Estimated One-Time Third-Party Disclosure Burden[1]

Type of Disclosure and 21 CFR Section	No. of Respondents	No. of Disclosures	Total Annual	Average Burden per	Total Hours	Total Capital, Operating

		per Respondent	Disclosures	Disclosure		and Maintenance Costs
Distribution of prescribing information by fax, email, or mail when requested (§§ 201.100(c)(5) and 201.100(g))	993	130	129,090	1	129,090	$26,500 to $90,750

C. Other Annualized Cost Burdens to Respondents: Operating and Maintenance Costs of the Toll-Free Telephone Number and Responding to Requests

This proposed rule would require that manufacturers provide and maintain a toll-free telephone number that users of prescribing information can call if they want the prescribing information to be faxed, emailed, or mailed to them. It was assumed that all manufacturers would use existing telephone infrastructure, and they would need to add options to the system so that someone could request the prescribing information in other forms, particularly if Internet access is not available. The costs would include labor costs to modify the phone system and to respond to requests. We will adopt the estimate for the annualized cost to have a functioning system and maintaining it from the economic impact analysis. The recurring annual costs to operate and maintain the toll-free telephone number and to send paper prescribing information upon request would range from $26,500 to $90,750 (Ref. 6). An average of this range will be used for this estimation, resulting in $58,619 per manufacturer.

Concerning the distribution of prescribing information by fax, email, or mail when requested (§§ 201.100(c)(5) and 201.100(g)), and based on data described in section IX.H of the Analysis of Impacts, we estimate that each manufacturer, repacker, relabeler, or contract manufacturer will receive approximately 130 requests annually to distribute prescribing information by fax, email, or mail, and that each distribution of prescribing information would take approximately 1 hour (table 4). In addition, we estimate that each request to receive prescribing information by fax, email, or mail will take approximately 15 minutes (table 1).

12b. Annualized Cost Burden Estimate

(1) There are labor costs associated with the estimated 33,390,126 annual reporting hours described above. Assuming an industry loaded wage rate of approximately $85 per hour, we estimate these costs to be approximately $2,838,160,710.

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Pharmaceutical industry average wage grade for preparing and submitting this information collection	33,390,126	$85.00	$2,838,160,710
Total			

(2) Estimated Cost Savings To Providers of Prescribing Information Would Range from $93.8 million to $216.6 million.

The proposed rule would require the electronic distribution of prescribing information (instead of the paper version with the drug product) for human prescription drugs and biological products. Electronic distribution would ensure that the most current prescribing information is available so that health care professionals can readily access the information and be better informed at the time of clinical decision-making and dispensing. Manufacturers and applicants would distribute prescribing information electronically by submitting the labeling to FDA in an electronic format that FDA can process, review, and archive (currently SPL format). The submitted labeling would be distributed via FDA's labeling repository Web site (labels.fda.gov), which is a publicly available Web site. The proposed rule would also require the immediate container label and outer container of human prescription drugs to bear a statement explaining that the most current prescribing information is available at FDA's labeling repository Web site (labels.fda.gov) and to provide a toll-free telephone number that health care professionals may use to request that the manufacturer or applicant send current prescribing information through alternative means, such as FAX, email, or mail. In cases where the immediate container label does not have adequate space for the statement, the statement would be required to be affixed to the immediate container by other means such as a peel back label.

The current system of requiring the paper form of prescribing information to physically accompany prescription drugs has led to the continued dissemination of out-of-date prescribing information. A single electronic labeling repository for prescribing information accessible to all users would ensure that those accessing it have the most up-to-date version.

The proposed rule would affect those responsible for creating and providing the content of the prescribing information and also the users of the prescribing information. Providers of prescribing information (i.e., drug manufacturers, including contract manufacturers, repackers, relabelers, and manufacturers or repackers of private label drugs, as well as manufacturers of blood and blood component products) would incur short-term costs to put new labels on the products' immediate container label and outer container or package. In the long run, however, their costs of producing prescribing information will decrease because these manufacturers would no longer need to provide it in paper form. The users of prescribing information (i.e., health care professionals, mainly physicians and pharmacists) could incur both short-run and long-run costs as a result of the proposed rule. The short-run costs would result from acquiring extra computers or printers where necessary. The long-run costs would result from the costs to print the prescribing information when necessary and the need for greater search time or interruption in workflow for pharmacists.

For providers of prescribing information, the proposed rule would require revising the product label on the immediate container label and any outer container or outside package to include a statement that directs users to FDA's labeling repository Web site to access current prescribing information and a toll-free telephone number for requesting alternative options for obtaining the prescribing information. The total one-time costs for providers of prescribing information would range from $191.4 million to $326.7 million and the total annual costs would range from $5.5 million to $20.5 million. Changing the immediate container label and outer container or package accounts for most of the one-time costs, and the impact per firm would vary based on the number of SKUs. The majority of the recurring costs would be for using nonstandard labels on immediate container labels or outer container or packages that

are too small to accommodate the proposed label statement containing the link to the FDA's labeling repository Web site address and the toll-free telephone number.

Providers of prescribing information would realize substantial savings from no longer having to print and store the paper form of prescribing information. Average costs to print and fold the paper forms of prescribing information range from $0.03 to $0.07 and the storage cost per SKU ranges from $1.40 to $1.50, based on storage costs of about $5 per square foot. There would also be savings from no longer losing labeling inventory when there are changes to the prescribing information. For the entire industry, annual cost savings would range from $93.8 million to $216.6 million.

Savings to Providers of Prescribing Information (in millions)

	Small Manufacturers of Branded Drugs		Large Manufacturers of Branded Drugs		Generic Drug Manufacturers		Repackers, Relabelers, and Products for PLDs		Total	
	Low	High	Low	High	Low	High	Low	High	Low	High
Number of Firms	163	207	156	198	232	295	900	1300		
Number of SKUs	7,500	12,500	7,500	12,500	15,000	25,000	120,000	150,000		
Number of PIs Produced Annually (millions)	59.7	80.7	238.7	322.9	298.4	403.7	1,613.3	2,182.7		
Annual Storage Cost per Insert	$1.40	$1.40	$1.50	$1.50	$1.50	$1.50	$1.40	$1.40		
Storage Costs	$10,500	$17,500	$11,250	$18,750	$22,500	$37,500	$168,000	$210,000		
Printing & Folding (millions)	$2.7	$6.1	$8.1	$20.7	$10.1	$25.8	$72.6	$163.7		
Total Annual Savings (millions)	**$2.7**	**$6.1**	**$8.1**	**$20.7**	**$10.2**	**$25.9**	**$72.8**	**$163.9**	**$93.8**	**$216.6**

The difference between the annual savings and annualized costs would be a net annual savings to providers of prescribing information of $61.0 million to $149.6 million at the 7 percent discount rate and $65.9 to $157.8 at the 3 percent discount rate.

For potential users of the prescribing information, the total one-time and recurring costs would range from $7.2 million to $18.6 million. Annual costs range from $45.4 million to $86 million. The estimated costs were driven by delays in accessing and printing and the number of units of prescribing information that would be printed rather than read on a computer screen. Annualized one-time costs over 10 years range from $1.0 million to $2.6 million at the 7 percent discount rate and from $0.8 million to $2.2 million at a 3 percent discount rate. The total annualized costs are the sum of the annualized one-time costs and the annual costs, and range from $46.4 million to $88.7 million at the 7 percent discount rate and from $46.2 million to $88.2 million at a 3 percent discount rate.

Summary for providers and potential users. The proposed rule would have an annualized net savings of $5.0 million to $73.5 million at a 7 percent discount rate and $10.0 million to $82.2 million at a 3 percent discount rate. The savings that the proposed rule would generate are because providers of the prescribing information would no longer have to print the paper version. The remaining printing would be done by individual users of the prescribing information, who would only print on an as-needed basis. The large range of the estimated impact of the rule reflects not only the uncertainty around some of the estimates but also the large number of entities affected: From 1,450 to 2,000 firms providing prescribing information and 150,000 to 200,000 SKUs needing new labels on the immediate container within 2 years of a final rule. A large number of potential users of prescribing information would also be affected by the proposed rule, including about 66,000 retail and hospital pharmacies and about 380,000 physicians who prescribe drugs. With such a large cohort, even small differences in estimates can create large differences in the totals. Electronic distribution of prescribing information would be new to all parties, and it is difficult to predict how pharmacists, physicians, and other users would react over time or to predict what new technologies may develop as a result of the change. Users would become more familiar with reading on screen and may not need to print prescribing information as often. In addition, new technological solutions may develop over time to simplify access to the prescribing information.

Summary of Annualized Costs and Cost Savings of the Proposed Rule (in millions)

	7% discount rate, 10 years	3% discount rate, 10 years

	Low	High	Low	High
Savings (net) to providers of prescribing information	**$51.8**	**$162.7**	**$56.6**	**$170.8**
Costs to Users	$46.4	$88.7	$46.2	$88.2
Costs to Blood Manufacturers	$0.4	$0.5	$0.3	$0.4
Net Savings	**$5.0**	**$73.5**	**$10.0**	**$82.2**

13. Other Annualized Cost Burdens to Respondents

1. Operating and Maintenance Costs of the Toll-Free Telephone Number

This proposed rule would require that manufacturers provide and maintain a toll-free telephone number that users of prescribing information can call if they want the prescribing information to be faxed, emailed, or mailed to them. It was assumed that all manufacturers would use existing telephone infrastructure, and they would need to add options to the system so that someone could request the prescribing information in other forms, particularly if Internet access is not available. The costs would include labor costs to modify the phone system and to respond to requests. We will adopt the estimate for the annualized cost to have a functioning system and maintaining it from the economic impact analysis. The recurring annual costs to operate and maintain the toll-free telephone number and to send paper prescribing information upon request would range from $26,500 to $90,750. An average of this range will be used for this estimation, resulting in $58,619 per manufacturer.

D. Capital Costs

There are no capital costs associated with this collection of information since:

Manufacturers are currently required to submit the labeling information to the FDA in an electronic format, so no new equipment or personnel would be needed, and 2) although the label would require a new statement to be included, the compliance date for the proposed rule would not go into effect until 2 years after the final rule publishes. This time frame will allow for those products that are already in

distribution to be exhausted and the manufacturer who markets the product can incorporate the new statement at the time of the next printing of labels for the immediate container label and outside packages.

14. Annualized Cost to the Federal Government

Generally, the costs to FDA to review this information collection would be covered under the Federal costs approved under OMB Control Number 0910-0001 and 0910-0338.

15. Explanation for Program Changes or Adjustments

This is a new proposed rule.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

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

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.