

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 606, and 610

[Docket No. FDA-2007-N-0363]

RIN 0910-AG18

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its prescription drug and biological product labeling regulations to require electronic distribution of the prescribing information intended for health care professionals, which is currently distributed in paper form on or within the package from which a prescription drug or biological product is dispensed. FDA is also proposing that prescribing information intended for health care professionals will no longer be permitted to be distributed in paper form with the package from which a prescription drug or biological product is dispensed, except as provided by this regulation. We are proposing these actions to help ensure that the most current prescribing information is publicly accessible for the safe and effective use of human prescription drugs.

DATES: Submit either electronic or written comments on the proposed rule by March 18, 2015. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by January 20, 2015 (see the “Paperwork Reduction Act of 1995” section of this document). See section XI for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments, by any of the following methods, except that written comments on information collection issues under the Paperwork Reduction Act of 1995 must be faxed to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to oir_submission@omb.eop.gov (see the “Paperwork Reduction Act of 1995” section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Docket No. FDA-2007-N-0363 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Emily Gebbia, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6217, Silver Spring, MD 20993, 240-402-0980.

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Executive Summary

Purpose of the Regulatory Action

The Food and Drug Administration (FDA) is proposing to amend its labeling regulations at 21 CFR 201.100, 201.306, 201.310, 606.121, 606.122, 610.60, and 610.61 for human prescription drugs and biological products, and blood and blood components intended for transfusion, to require that the prescribing information intended for health care professionals be distributed electronically and, with few exceptions, not in paper form. Prescribing information provides health care professionals the information necessary for the safe and effective use of the product. It is updated periodically to include the most current information, such as newly acquired safety information. Currently, the prescribing information is distributed in paper form on or within the package from which a prescription drug is dispensed. The paper form of the prescribing information may not contain the most current information because it may have been printed and distributed prior to more recent labeling changes, while the electronic form of prescribing information can be updated in real-time. FDA is taking this action to ensure that the most current prescribing information for prescription drugs will be available and readily accessible to health care professionals at the time of clinical decisionmaking and dispensing. The electronic distribution requirements of this proposed rule would not apply to patient labeling

(including patient package inserts and Medication Guides), or to prescribing information accompanying promotional labeling, which would continue to be provided in paper form.

FDA is authorized under various sections of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to require that prescribing information be distributed electronically and to require that paper copies of the prescribing information no longer be distributed, except as provided in this regulation, to ensure that human prescription drugs have adequate directions for use and to ensure the efficient enforcement of the FD&C Act. These sections include sections 201(n), 502, 503, 505, and 701(a) of the FD&C Act (21 U.S.C. 321(n), 352, 353, 355, and 371(a)), and section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). The electronic distribution of prescribing information for human prescription drugs would permit the efficient enforcement of the misbranding provisions in sections 502(a) and (f) of the FD&C Act, as well as the safety and effectiveness provisions of section 505 of the FD&C Act.

Summary of the Major Provisions of the Regulatory Action

The proposed rule would amend the labeling regulations to require manufacturers to distribute the prescribing information electronically, instead of in paper form. Manufacturers would be required to submit the prescribing information to FDA for posting on FDA's publicly available labeling repository Web site

(labels.fda.gov) every time there is a change in the labeling. Manufacturers would also be required to review the labeling posted at FDA's Web site to verify that the correct version of the labeling appears in the repository, and to promptly notify FDA if the correct version is not posted. This would ensure that the most up-to-date version of the prescribing information is available to health care professionals and the public.

The proposed rule would require a product's immediate container label and outside package to bear a statement directing health care professionals to FDA's labeling repository to view the electronic version of prescribing information. The statement would also provide a toll-free telephone number, maintained by the manufacturer, to receive requests for the manufacturer to send an emailed, faxed or mailed paper copy of the prescribing information. The manufacturer would be required to ensure the toll-free number service was available 24 hours a day, 7 days a week. This would ensure that the prescribing information is accessible in most situations when Internet access is not available to the health care professional.

In addition, the proposed rule would provide that FDA may grant an exemption from the electronic distribution of labeling requirements when compliance could adversely affect the safety, effectiveness, purity, or potency of the drug, is not technologically feasible, or is otherwise inappropriate. Manufacturers of exempted products would distribute

prescribing information in paper form on or within the package from which the product is dispensed. Examples of circumstances where it may be appropriate to exempt a product include a product intended for use in an emergency room or a product that may be stockpiled for an emergency.

Costs and Benefits

The proposed rule impacts the drug and biological products industries that supply prescribing information, as well as the prescribers, pharmacists and other health care professionals who are the intended users of the information. After initial set-up costs, industry will experience net savings by providing the prescription information electronically. Pharmacies will incur net costs due to initial capital costs to access the information, increased search time when accessing the information and the printing cost when a request is received for the prescribing information in printed form. We estimate no cost increases to most health care professionals to access the information.

At a 7 percent discount rate over a 10-year period, the annualized cost savings range from \$52 million to \$164 million and are predominantly savings to industry; the annualized costs range from \$47 million to \$89 million and are mainly incurred by pharmacies; and the annualized net savings range from \$5 million to \$74 million. The public health benefits of users having access to the most up-to-date version of the prescribing information have not been quantified.

SUMMARY OF ANNUALIZED COSTS AND COST SAVINGS OF THE PROPOSED RULE
[\$ millions]

	7% discount rate, 10 years		3% discount rate, 10 years	
	Low	High	Low	High
Cost Savings	\$51.8	\$163.7	\$56.6	\$170.8
Costs	46.8	89.2	46.6	88.6
Net savings	5.0	73.5	10.0	82.2

I. Background

We are proposing to amend the labeling regulations to require electronic distribution of prescribing information for human prescription drugs.¹ 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 health care professionals at the time of clinical decisionmaking 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 health care professionals, consumers, and/or the public. These initiatives include the electronic prescribing provisions of the Medicare Prescription Drug Improvement and Modernization Act (Pub. L. 108-173), 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

¹ When used in this proposed rule, the term "drug" includes biological products *e.g.* allergenic products, vaccines, blood and blood components intended for transfusion, plasma derivatives, gene therapies, and human cells, tissues, and cellular- and tissue-based products licensed under section 351 of the PHS Act.

listing of drug products. Additionally, the Agency has been involved in an initiative known as “DailyMed”. “DailyMed” is a publicly-available, computerized repository of a broad array of drug information, which is maintained by the National Library of Medicine.

A. How do “Prescription Drug Labeling”, “Prescribing Information”, and “Patient Labeling” for human prescription drugs differ?

“Prescription drug labeling,” as relevant to this proposed rule, includes prescribing information; patient labeling; the product’s immediate container label; outer container; the outside package; and other written, printed, or graphic information that accompanies the product. Prescription drug labeling meets the definition of “labeling” in section 201(m) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(m)) and must comply with all applicable provisions of section 502 of the FD&C Act (21 U.S.C. 352). In addition, in order to be exempt from the statutory requirement of section 502(f)(1) of the FD&C Act, prescription drug labeling must also satisfy the requirement of § 201.100(d) (21 CFR 201.100(d)) which states that any labeling, as defined in section 201(m) of the FD&C Act, whether or not it is on or within a package from which the drug is to be dispensed, distributed on or behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug contains adequate information for such use, as further described in that provision. In this document, the terms “prescription drug labeling”, “product labeling”, and “labeling” will be used interchangeably as broader terms to encompass prescribing information and other information considered to be components of labeling. All components of labeling are submitted to FDA as part of an applicant’s new drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA), supplement, annual report, or in other submissions, such as establishment registration and drug listing.

“Prescribing information”, commonly referred to as “professional labeling”, “content of labeling”, “package insert”, “physician labeling”, “direction circular”, “circular of information”, or “package circular”, is a component of prescription drug labeling and is periodically updated to include the most current information about the

product. For products approved by FDA, approval of the prescribing information is based on the Agency’s thorough analysis of the marketing application, including the proposed label, submitted by the applicant. Prescribing information contains the information necessary for safe and effective use of the product, and is intended for use by the health care professional. Prescribing information is subject to the format and content requirements of §§ 201.56, 201.57, 201.80, 606.122, or 610.61 (21 CFR 201.56, 201.57, 201.80, 606.122, or 610.61). Prescribing information is currently distributed in paper form with the product to meet the condition stating that labeling on or within the package from which a prescription drug is to be dispensed bears adequate information for its use (§ 201.100(c)(1)). This proposed rule applies to prescribing information that is currently distributed in paper form on or within the package from which the prescription drug is to be dispensed. In addition, prescribing information must also accompany “promotional” labeling, as described in § 202.1(l)(2) (21 CFR 202.1(l)(2)).² This proposed rule will not apply to prescribing information that accompanies promotional labeling, which will continue to be distributed in paper form. Therefore, we propose new § 201.100(d)(4) to make clear that prescribing information accompanying promotional labeling must be distributed in paper form.

“Patient labeling”, another component of labeling for some prescription drugs, is FDA-approved information that is intended for patient use and includes patient package inserts and Medication Guides. Patient labeling must be reprinted in the prescribing information or must accompany the prescribing information (§§ 201.57(c)(18) and 201.80(f)(2)). Because FDA is examining methods to improve the content and distribution of patient labeling in a different initiative,

² Such labeling is described in § 202.1(l)(2) and includes, for example, printed, audio, or visual matter containing drug information supplied by and disseminated by or on behalf of the manufacturer, packer, or distributor. Examples include but are not limited to: Brochures, booklets, mailing pieces, calendars, price lists, catalogs, letters, motion picture films, sound recordings, exhibits, or literature. Such promotional material is labeling as defined in section 201(m) of the FD&C Act, and therefore, must comply with § 201.100(d) which states that any labeling, as defined in section 201(m) of the FD&C Act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug contains adequate information for such use.

patient labeling is not affected by this proposed rule and will continue to be provided in paper form, as required by applicable regulations, and to be electronically submitted to FDA with the prescribing information. Therefore, for those products including patient labeling, patients will continue to receive warnings, risk information, and special instructions for use in paper form as patient labeling.

Prescription drug labeling also includes the product’s immediate container label and the outside package. It is noted that labeling regulations of biological products distinguish between a “container label” and “package label” (§§ 610.60 and 610.61 (21 CFR 610.60 and 610.61)). For purposes of this document, any reference to the “outside package” applies to the “package label” for biological products or the outer carton, outer container, or outer package of the prescription drug. Based on the FD&C Act definitions of the terms “label” and “labeling”, any outer container, carton, or package is “labeling”.

B. Who receives paper prescribing information and who uses it?

The prescribing information that is the subject of this proposed rule is the paper version that is on or within the package from which the drug is to be dispensed (e.g., physically attached to the bottle containing the drug, inside the carton or box containing the drug, with the bulk pharmacy package). Usually, it is printed on thin paper in small size font, and is folded multiple times so that it can be contained within the drug carton or can be otherwise attached to drug packaging. Drug products, with the paper prescribing information on or within their packaging, are distributed to pharmacies for dispensing.

This paper prescribing information is intended for use by all health care professionals. However, health care professionals have come to rely on electronic or other paper versions (e.g., compendia such as the Physicians’ Desk Reference (PDR)) compiled by third parties instead of this paper version. Prescribing physicians and many health care professionals (e.g., nurses) typically do not receive this paper version because they do not dispense drugs. Pharmacists do receive it along with the drug product from the manufacturer or distributor, but it is often difficult to read due to the small font size, thin paper, and multiple folds, and we have heard anecdotally that it is often discarded. In addition, pharmacies usually have some form of compendia purchased from a third party, and many

hospitals and chain pharmacies rely on electronic compendia. Patients ordinarily do not receive the paper prescribing information because the pharmacist dispenses the drug to a patient in a different container than the packaging from the manufacturer, but they do receive other information intended for patients from the pharmacy (see section I.A).

C. Discussion of Special Consideration of Types of Human Prescription Drug Labeling

1. Instructions for Use for the Pharmacist

Instructions for use for the pharmacist are considered part of human prescription drug labeling, specifically part of the prescribing information. For the purposes of this proposed rule, instructions for use for the pharmacist include any instructions for administering, assembling, reconstituting, mixing, diluting, or other preparation that is done prior to dispensing the drug product to the patient. These preparation steps for the pharmacist are contained in the “Dosage and Administration” section of the prescribing information (§§ 201.57(c)(3) and 201.80(j)), which currently accompanies the product in paper form. If the information is adequately concise, it may also be printed on the product’s immediate container label or on the outside package. To the extent that this information is available on the immediate container label or outside package, it does not fall within the scope of this proposed rule. However, usually the product’s immediate container label is too small to contain the preparation instructions, so the immediate container label or the outside package typically bears a statement referring to the prescribing information for the detailed instructions. Therefore, where the container label refers to the prescribing information for preparation instructions, this proposed rule would require that these instructions for use for the pharmacist be available electronically, rather than in paper form. This proposed rule provides a mechanism, if needed, to request the prescribing information in paper form. FDA welcomes comments on whether, in circumstances where the instructions for use for the pharmacist are not sufficiently concise to be printed on the immediate container label or outside package, the electronic version of the prescribing information is adequate.

2. Prescribing Information (Circular of Information) for Blood and Blood Components Intended for Transfusion

In addition to § 201.100, blood and blood components intended for transfusion are also subject to labeling requirements under §§ 606.121 and 606.122, including the requirement that the circular of information be available for distribution, and to registration and listing requirements under 21 CFR part 607. This rule, if finalized, would require that the prescribing information (*i.e.*, the circular of information) for blood and blood components intended for transfusion be provided electronically, rather than in paper form. This rule would also provide the mechanism for a request to be made for prescribing information in paper form. In contrast to biological products that register and list under part 207 (21 CFR part 207), however, labeling and registration and listing information for blood and blood components are currently not electronically submitted to the Agency. FDA is in the process of developing standards for the electronic submission of labeling for these products, and these standards will eventually accommodate blood and blood components. The Agency will consider progress in developing such standards when setting a compliance date for blood and blood components and/or on our own initiative granting an exemption for blood and blood components for a period of time until electronic submission of the labeling for blood and blood components is supported. Thus, the final regulation may include staggered compliance dates, with a later compliance date for blood and blood components and an earlier compliance date for all other drug products. We also invite public comment on whether blood and blood components intended for transfusion should be subject to the electronic distribution of prescribing information requirements in this proposed rule once the electronic submission standards accommodate these products.

3. Access to Prescribing Information When Internet Access Is Unavailable

FDA recognizes that there may be situations that present challenges for accessing electronic prescribing information of prescription drugs. Some of these situations were identified in the July 2013 Government Accountability Office Report “Electronic Drug Labeling: No Consensus on the Advantages and Disadvantages of Its Exclusive Use” (GAO Report) (Ref. 1).

During a public health emergency, natural disaster, or other situation

involving field response, there may be power outages or technology service interruptions that render electronic prescribing information unavailable to health care professionals. Responders generally enter an emergency situation with all the medical supplies and materials necessary to address the emergency situation. Therefore, we do not anticipate that they would rely on the Internet being available to be able to provide medical care. For example, deployment units often have electronic medical resources that can be used with wireless mobile devices. If wireless service is not available, units are also equipped with back-up sources of drug information (*e.g.*, compendia downloaded onto laptops or tablets, paper compendia, and other targeted information to address the public health emergency). Responders also train extensively for emergency situations and are very familiar with the specific drugs they are dispensing, reducing the risks associated with not having access to the electronic prescribing information. Thus, reference to the full content of labeling would rarely be necessary in such an emergency. When it comes to natural disasters that affect pharmacies, they often have contingency plans in place for how services will be provided (*e.g.*, during events such as power disruptions). For example, some pharmacies may rely on back-up generators or refer patients to another nearby pharmacy (Ref. 1). We invite comment from public health authorities and the medical care community on how product labeling is currently handled and whether current practices are sufficient when Internet access is not available due to disasters or public health emergencies. We also invite comment on what impact, if any, this proposed rule will have during a public health emergency, natural disaster, or other situation involving field response when Internet or wireless access is not available or reliable.

We also recognize that, during the course of a declared emergency, FDA may issue an emergency use authorization for an unapproved use of an FDA-approved drug (21 U.S.C. 360bbb–3). In such a situation, it may be appropriate to direct health care providers to materials about the Emergency Use Authorization as the primary source of information about product use for and during the emergency, in addition to FDA-approved labeling available in the labeling repository or in paper form, as appropriate. We invite comment on whether the proposed exemptions provision provides emergency planners

with sufficient flexibility regarding the labeling of their stockpiled products.

We also are concerned that there may be health care providers that are routinely unable to access electronic prescribing information due to a lack of Internet access, either because of resource constraints or geographic location, *e.g.*, in rural areas with limited Internet access. As described in detail in section IV.B, we are proposing that such health care providers would be able to access current prescribing information through mail, fax, or email, by calling a toll-free number that would be required to be included on the immediate container label and outer container of human prescription drugs. In section IV.B, we invite comment on whether requesting the prescribing information over the telephone is a sufficient method for obtaining it when it cannot be accessed using the Internet. We also invite comment on alternative or additional methods for ensuring that health care professionals without regular Internet access have the most current prescribing information, including comment on other systems described in section II.C.

Finally, we note that drugs may be exported from the United States for humanitarian use in other countries. We expect that labeling for such products will often be in the language of the country to which it is being exported and include units of measurement used in or designated by the country to which the drug would be exported. Further, in some instances, the country to which a drug is being exported may have different or additional labeling requirements or conditions for use (compared to those on the FDA-approved labeling), and the foreign country may require the drug to be labeled in accordance with those requirements or uses. For these reasons, we expect that drugs intended for export generally will be labeled in accordance with the foreign requirements and conditions for use, as long as the conditions in the relevant provisions of the FD&C Act, or if applicable, section 351(h) of the PHS Act, are met. Nevertheless, we request comment on any impact that our current proposal to require the electronic distribution of labeling may have on drugs exported for humanitarian use and whether any modifications to the proposal should be made to address such products.

D. What is the history of electronic regulatory submissions?

On December 11, 2003, we 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 labeling review process and to provide more timely approval of labeling changes. To support this requirement, we issued guidance in April 2005 entitled “Providing Regulatory Submissions in Electronic Format—Content of Labeling” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072331.pdf>). This guidance describes the Structured Product Labeling (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 (Pub. L. 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 (manufacturers³) to submit drug establishment registration and drug listing information electronically unless an exemption 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 (§ 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, entitled “Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf>). 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 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, in June and December, if there have been changes to the listing elements in the prior 6 months (21 U.S.C. 360(j)(2)).

This proposed rule will complement FDA’s other electronic initiatives and is intended to improve access to up-to-date prescribing information for health care professionals, thereby enhancing the safe and effective use of prescription drugs.

E. Discussion of Other Labeling Initiatives

The final rule entitled “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products” (71 FR 3922; January 24, 2006) became effective on June 30, 2006 (the 2006 rule) (21 CFR parts 201, 314, and 601). The purposes of this final rule were to improve the management of the risks of medical product use and reduce medical errors by health care professionals, as well as enable health care professionals to better communicate risk information to their patients. The new content and format requirements make it easier for health care professionals to access, read, and use prescribing information, thereby increasing the extent to which they rely on it to obtain information on prescribing, dispensing, and administering prescription drugs. In announcing the final rule, FDA explained that these new requirements should enhance the safe and effective use of prescription human drugs and in turn reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information.

The 2006 rule only applies to applications or efficacy supplements approved since June 30, 2001; those pending on June 30, 2006; and to new applications and efficacy supplements submitted after June 30, 2006. There are older drug products that are not subject to the new labeling content and format requirements and that have a different format of labeling and may have different headings in the labeling. As proposed, this rule does not require the electronic versions of the labeling of these older drug products to comply with the content and format requirements of the 2006 rule. FDA invites comment on whether the existence of the two different formats of electronic labeling would present barriers to their value when used in the health care setting.

³ For the purposes of this proposed rule, the term “manufacturer” will be used to refer to manufacturers, repackers, relabelers, and private label distributors, unless otherwise stated. (See § 207.3(a)(8)).

II. Discussion

A. What are we proposing?

This proposed rule would require electronic distribution of prescribing information for human prescription drugs and biological products that meet the definition of a drug (see footnote 1) instead of the paper form. 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 decisionmaking and dispensing. This proposed rule would apply to manufacturers, applicants, and persons who market prescription drugs that they regard as not subject to section 505 of the FD&C Act (21 U.S.C. 355). Again, for ease of reference, in the preamble of this regulation, we will use the phrase “manufacturer or applicant” to refer to manufacturers, applicants (including holders of NDAs, ANDAs, and BLAs), and persons who market unapproved drugs. The proposed rule would require manufacturers and applicants to distribute electronically prescribing information by submitting the labeling in an electronic format that FDA can process, review, and archive (currently SPL format) to FDA each time the labeling content is changed. The submitted labeling would be distributed via FDA’s labeling repository Web site (labels.fda.gov), which is a publicly available Web site. By proposing to make the most current prescribing information available at a single, comprehensive Web site, the rule would address a concern raised by stakeholders and identified in the GAO Report regarding the limitations of the multiple Web sites that currently provide electronic labeling and the importance of having a single data source that is reliable, authoritative, and comprehensive (Ref. 1). The proposed rule also would 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 (e.g., U.S. Postal Service or other delivery service). 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. As described in further detail in section

IV.B, the only products that would not be required to bear the statement on both the immediate container and the outside package are biological products that are capable of bearing only a partial label or are incapable of bearing a container label.

Given the time necessary for industry to make preparations needed to comply with this regulation, FDA is proposing an effective date of 6 months after the publication date of the final rule in the **Federal Register** and a compliance date of 2 years after the date of publication of the final rule (see sections XI and XII for the compliance dates and implementation plans for this rule). FDA is requesting comments on the proposed effective and compliance dates, and whether they allow sufficient time for industry to implement this rule and, if not, how much additional time would be needed for implementation.

B. Why is electronic distribution of prescribing information better?

FDA has determined that requiring electronic distribution of prescribing information and eliminating the paper form that is contained on or within the package from which the drug is to be dispensed is important to ensure health care professionals have access to the most up-to-date information about the safe and effective use of the drug. To meet the requirement that states that labeling on or within the package from which the drug is to be dispensed bears adequate information for its use (§ 201.100(c)(1)), 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 outer 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 health care professional may not contain the most current information because, as described in II.B.1, the paper form accompanying the product may have been printed and distributed prior to more recent labeling changes.

1. Time for Updated Paper Form of Prescribing Information To Reach Marketplace

Paper prescribing information may be outdated by the time the drug product reaches pharmacy shelves. The manufacturer or applicant of a prescription drug may take 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 or applicants 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 outdated 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. FDA contracted with the consulting firm Eastern Research Group, Inc. (ERG) to investigate, among other things, how industry currently implements safety labeling changes and the associated timelines for making changes. ERG issued a report entitled “Analysis of the Feasibility of Safety Labeling Changes Implementation Timelines” that describes that it may be months, if not years, before updated prescribing information is available with finished drug product. It was estimated that, for printed prescribing information attached to a drug product, a change will generally reach the market anywhere from as little as 3 months to more than 39 months after the change is made (Ref. 2).

Such delays in updating the paper prescribing information raise concerns about health care professionals using outdated information for clinical decisionmaking. While not all changes may be related to significant safety or effectiveness concerns, some changes to the prescribing information are critically important for the safe use of the drug (e.g., a new contraindication or warning). Because drugs that are already in distribution are not generally recalled to update the prescribing information, this new risk information would not appear in the paper prescribing information, while it could be promptly incorporated in an electronic version.

2. Time for Updated Electronic Prescribing Information To Reach the Marketplace

Unlike the paper form, electronic prescribing information can be updated in real-time with newly acquired safety or effectiveness information, and would be available for use by prescribers and other health care professionals within days of an update. Currently, electronic forms of the prescribing information for many, but not all, human prescription

drugs, are available through various sources to health care 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 applicants and manufacturers distribute the drug's most current labeling electronically by submitting the prescribing information to FDA in a format that FDA can process, review, and archive each time the content is changed. These submissions will populate FDA's publicly available labeling repository so that the updated prescribing information is distributed in a timely fashion to prescribers, pharmacists, and health care providers. This proposed rule would require the manufacturer or applicant to verify that its prescribing information appears on FDA's labeling repository Web site and is accurate, complete, and up-to-date, and to notify FDA if the labeling is not promptly posted or if the labeling on FDA's labeling repository Web site is not accurate, complete, and up-to-date. Since FDA's labeling repository Web site will link prescribing information to specific National Drug Code (NDC) numbers, 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 NDAs, ANDAs, and BLAs, and those marketed and not approved.

C. Need for Up-To-Date Prescribing Information

Based on the availability of a complete source for up-to-date electronic prescribing information upon implementation of this regulation, coupled with much higher use of electronic systems in health care, FDA concludes that the time is right to transition to electronic distribution of prescribing information from the static, potentially outdated paper version on pharmacy shelves. A recent survey of 436 pharmacists was conducted to assess pharmacists' readiness to adopt "paperless labeling" (*i.e.*, electronic prescribing information) (Ref. 3). Among this sample of pharmacists from chain pharmacies, independent retail pharmacies, hospitals, and other rural or urban dispensing sites, approximately 79 percent of respondents believed that paperless labeling would improve the adequacy of drug information available

in their worksite and most pharmacists believed that patient safety would improve as a result because updated information about a drug would be readily accessible. Most pharmacists also reported that communication with patients would improve as a result of a paperless system as 81 percent of pharmacists reported using prescribing information when educating or counseling patients and verifying dose information. Pharmacists participating in the survey, in all settings except chain pharmacies, reported relying on manufacturer Web sites for online prescribing information. Pharmacists of chain pharmacies reported using corporately curated prescribing information. Of all pharmacists surveyed, only 6 percent reported using exclusively paper resources to retrieve prescribing information and only 4 percent did not have Internet access.

In addition, as described in this document, at present there are delays between when the labeling change occurs and when a product with the updated paper copy of the prescribing information actually reaches the pharmacy or point of care. During our public meeting in 2007 (see 72 FR 15701; April 2, 2007), described in section III, we heard that this is a concern of many health care professionals and consumers. Health care professionals and representative organizations believed that having the most up-to-date prescribing information would allow them to make better informed clinical decisions for their patients and would benefit the public health overall.

FDA tracks safety labeling changes and classifies them by type, depending on the risk described and the section of the prescribing information that is changed. Based on 11 years of data (2003 to 2013), we determined that there are approximately 500 safety labeling changes made each year (Ref. 4). Postapproval, 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. In general, when important new safety information has been acquired, a new boxed warning may be added to the prescribing information to alert prescribers about the new serious risk. Our regulations also require that the boxed warning information be explained in more detail in the "Contraindications" or "Warnings and Precautions" sections of the labeling (§ 201.57(c)(1)). Therefore, addition of a new boxed warning or changes to the

boxed warning generally will also affect more than one section of the prescribing information.

We conducted an internal review of labeling changes for new molecular entities, a small subset of all marketed prescription drugs, for the calendar years of 2005 to 2007, and found 36 new boxed warnings were added to the prescribing information during this 3 year period (Ref. 5). 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, nonsteroidal anti-inflammatory drugs, and atypical antipsychotics.

In addition to boxed warnings, there are many other safety-related changes to other sections of the labeling that will add new information that is important for patient care. For example, changes to the "Contraindications" section can affect prescribing decisions and the patient population eligible for the drug, while changes to the "Warnings and Precautions" section and "Adverse Reactions" section can affect patient monitoring or management. We conducted an internal review of changes made to the boxed warning and "Contraindications" sections between the years 2003 to 2013 and found that there are about 50 additions or changes to boxed warnings each year and about 60 changes to the "Contraindications" section (Ref. 4). For example, in 2013, the prescribing information for codeine products (including all generic products containing codeine) was revised to include a new boxed warning and an addition to the "Contraindications" section to inform prescribers of the risk of respiratory depression and death in children who underwent tonsillectomy and/or adenoidectomy related to ultra-rapid metabolism of codeine to morphine. That same year, FDA issued a safety announcement regarding the use of valproate drug products for pregnant women taking the drug for migraine prevention and the prescribing information was updated to add new information to the boxed warning to inform prescribers that use of the drug while pregnant can cause major congenital malformations, particularly neural tube defects such as spina bifida, and decreased IQ scores in children. The serious nature of these warnings highlight the need for health care professionals to have access to, and utilize, the most current prescribing information from a reliable and consistent source.

FDA has tentatively concluded that health care professionals should have

access to, and rely on the most updated prescribing information when making prescribing or other clinical decisions about the safe and effective use of a drug. For this reason, FDA considered a mandatory dual system for distribution of prescribing information (*i.e.*, one in which both paper and electronic versions would be distributed simultaneously). Under such a system, the paper version of the prescribing information could include a statement that would notify the health care professional that the paper version may not contain the most up-to-date information and would direct the health care professional to the electronic version. FDA is concerned that, even with this statement, the potentially outdated paper version may be used to make a decision impacting patient care. If the paper prescribing information remains available, a busy health care professional may not look to the labeling repository to ensure he or she is reading the current paper version of the prescribing information or to ascertain what section of the prescribing information has been updated since the paper version was printed. A health care provider who does not have Internet access may continue to rely on an outdated paper version of the prescribing information, rather than contacting the manufacturer for the most updated version.

FDA also considered a dual system that requires the electronic version of the prescribing information and permits voluntary distribution of the paper version. In addition, to the concerns we describe previously with a mandatory dual system, FDA is concerned that a voluntary dual labeling system could cause confusion and workflow disruptions for health care professionals where it would be left to each manufacturer's discretion to decide whether its products will be distributed with the paper version of the prescribing information.

One additional system that FDA is soliciting comment on is a system that requires manufacturers to distribute the prescribing information electronically, as described in this proposed rule. Where paper prescribing information is needed, dispensers (*e.g.*, pharmacies) would have the option of ordering single or multiple copies of the paper prescribing information when ordering a shipment of drug from the distributor. The distributor, or other entity that delivers the drug to a dispenser, would be required to provide the paper prescribing information in the quantity ordered along with the shipment of the drug to the dispenser. The manufacturer would be required to provide sufficient

numbers, or a means to produce sufficient numbers, of the paper prescribing information to the distributor. With this option, for the reasons described previously, FDA does not anticipate that dispensers would routinely order paper prescribing information because they would rely on the electronic version of the prescribing information and because pharmacies usually have some other form of compendia purchased from a third party. Nevertheless, this option would permit dispensers to receive paper prescribing information with drug shipments, as needed.

We seek comment on the dual systems described previously. Specifically, we request comment on whether and how dual systems could achieve the goal of ensuring that health care providers have the most current prescribing information. We also request comment on the structure of a dual system (*e.g.*, if such a system should require both a paper and electronic version be distributed, or require the electronic version while allowing the paper version to be distributed voluntarily or ordered by dispensers), what kind of statement the paper prescribing information should contain to advise health care providers about the electronic version, and if there are concerns or benefits not identified by FDA with such an approach. With respect to the system that would provide the dispenser the option of ordering paper prescribing information, we request comment on any challenges, including administrative challenges, to manufacturers, distributors, or dispensers related to an ordering and fulfillment process for paper prescribing information. Finally, we note that a system in which paper copies could be ordered from the distributor could address concerns discussed in section I.C.3 about health care providers that do not have reliable regular Internet access and we invite comment on this aspect of a system.

The GAO Report noted that a potential disadvantage of the exclusive use of electronic prescribing information is that it could disrupt pharmacists' workflow by requiring different steps for pharmacists to use to consult prescribing information and also preventing them from retrieving the prescribing information from the box when the pharmacist felt it was necessary to show it to the patient during a consultation (Ref. 1). The GAO Report said that these workflow disruptions could reduce the time available for patient consultations and noted that interruptions to pharmacists' workflow have been shown to increase

the risk of errors made when dispensing a drug. We are aware that transitioning from a paper to electronic delivery system for prescribing information may be a change in practice that may require adjustments. In addition, if a pharmacist determines that accessing electronic prescribing information would be too disruptive, the pharmacist might instead rely on memory or outdated prescribing information available to the pharmacist in paper format, *e.g.*, in a paper-based compendia. We note, however, that in the recent survey of pharmacists discussed previously, most reported that a paperless system would improve patient safety and communication with patients (Ref. 3). Further, some of the workflow disruptions that a paperless system might cause could be offset by the advantages of having electronic prescribing information. For example, as noted in the GAO Report, in comments, and in public testimony received by FDA, electronic prescribing information is more user-friendly than the current paper package inserts: Pharmacists can quickly identify the information they are seeking by using hyperlinks and can adjust the font size to make it easy to read. We request comment on the potential workflow disruptions associated with a switch to an online-only system, and any related risks to the public health. We also request comment on whether the effective and compliance dates described in sections XI and XII of this proposed rule should be modified to allow for more time to adapt to workflow changes and to mitigate any potential risks caused by changes in workflow resulting from the proposed rule.

D. How are the application processes for changes to labeling affected?

This 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 pending FDA approval, and editorial changes that may be submitted in the annual report. Any postapproval labeling changes to an application (NDA, ANDA, or BLA) must comply with §§ 314.70, 314.97, or 601.12, as applicable, and under those requirements FDA would continue to be notified about supplements and other changes to approved applications (§§ 314.70(a) and 601.12(a)). Depending on the type of change, the changes would continue to be submitted as a supplement for prior approval ("prior approval supplements") before

distribution, as a Changes Being Effected (CBE) supplement, or by inclusion of the information in the annual report (§§ 314.70(b), (c), and (d); 314.81(b)(2); 601.12(b), (c), and (d)). (See, also section IV.E. "Submission of Most Current Version of Prescribing Information to FDA" for more information.)

This proposed rule would require manufacturers and applicants to distribute labeling electronically via posting on FDA's labeling repository. We propose to require submission of the prescribing information, in a format that FDA can process, review, and archive for distribution via the FDA's labeling repository Web site. Generally, it is expected that labeling can be posted as early as the next business day following its submission to FDA. In the case of a labeling change submitted in a prior approval supplement, the proposed regulation would require applicants to submit the labeling within 2 business days following FDA approval of the supplement.

For changes contained in a CBE supplement, the labeling should be submitted to FDA on the same day that a CBE supplement is submitted to the Agency. Minor changes to the prescribing information that would normally be documented in the applicant's annual report to 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 Web site. This will help to ensure that the most current labeling is considered by FDA and available to the public.

III. Public Hearing on the Electronic Distribution of Prescribing Information

A. Summary of Comments

In the **Federal Register** of April 2, 2007 (72 FR 15701), we 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. We 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 at 15702). At the public hearing, we explained that FDA 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 health care 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 health care professionals if FDA converts to electronic distribution of prescribing information.

- There are varying opinions as to whether FDA should require electronic distribution of prescribing information for all prescription drugs, whether there should be a transition period whereby paper forms would coexist 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 in emergency situations resulting in a loss of electricity or Internet access arose. Some suggested that we should create an annual compendium that health care professionals could consult as a backup resource.

B. FDA's View on the Comments and Testimony

We considered these comments in drafting this proposed rule. For example, FDA agrees that electronic distribution of prescribing information should give health professionals access to the latest information for a particular human prescription drug and contribute to improving patient care. The paper prescribing information that is the subject of this proposed rule is the version that is on or within the package from which the drug is to be dispensed

(e.g., the bulk pharmacy package). In general, prescribing physicians do not dispense drugs, so they usually do not have access to the paper version appended to the bulk pharmacy package. Instead, they use electronic or paper versions (e.g., compendia such as the Physicians' Desk Reference (PDR)) and would have access to FDA's labeling repository. Pharmacists that currently use the paper prescribing information will need to seek drug information by accessing FDA's up-to-date electronic labeling repository or by requesting the paper version of the prescribing information from the manufacturer or, if needed, consulting another source (e.g., paper or electronic compendia). Patients generally do not receive the paper prescribing information, but they would also have access to up-to-date electronic prescribing information from FDA's labeling repository Web site. 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.

We also agree that electronic distribution of prescribing information may reduce waste. We have heard anecdotally that the paper form of prescribing information is not generally used and is frequently discarded with the drug packaging to conserve shelf space in the pharmacy. However, we 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.

We also agree that electronic prescribing information is more user-friendly. Pharmacists have stated that the paper version is very difficult to read because of small font sizes and hard to keep organized once it is unfolded. The user of an electronic version would have ability to make the print larger and easier to read, and to navigate the prescribing information through the use of hyperlinks.

This proposal represents a continuation of our efforts to improve access to prescription drug labeling and to make a transition from paper to electronic distribution of prescribing information so that health care providers utilize the most up-to-date version of the prescribing information. To help understand the impact of this proposed rule, we invite any additional comments on the use of prescribing information by prescribers and other health care professionals, as well as consumers/patients.

IV. Description of the Proposed Rule

A. Labeling Accompanying the Product

Section 201(m) of the FD&C Act defines “labeling” to mean “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” For purposes of this rulemaking only, we consider electronic distribution of prescribing information to be “accompanying” the drug, through the label statement directing interested parties to access the prescribing information through the Internet or other electronic means.

B. Label Statement

Proposed §§ 201.100(b)(8) and 610.61(t) would require a statement to appear on the immediate container label (or be affixed to the immediate container by other means such as a peel-back label) and the outer container or package stating that to obtain the current prescribing information, go to labels.fda.gov or call (insert the toll-free telephone number) for a faxed, emailed, or mailed copy. In order to ensure that it is readable, the statement would be required to be no smaller than 6-point type.

Proposed § 610.60(a)(8) would require biological product containers capable of bearing a full label to bear the statement. However, we do not propose to amend § 610.60(c) or (d) to require the statement to appear on the container label or to be affixed to the immediate container by other means for containers that bear only a partial label or no container label. Consistent with current § 610.60(c) and (d) and proposed § 610.61(t), containers capable of bearing only a partial label and containers incapable of bearing a label must be placed in a package that must have a label bearing the required statement detailed in this proposed rule. FDA recognizes that the package may be discarded at the time containers are stored and invites comment on the availability of the package in cases where the immediate container label does not have adequate space for the required statement.

Proposed § 606.121(c) would require the container label of blood and blood components to bear the statement: See circular of information for indications, contraindications, cautions, and methods of infusion. To obtain the current circular of information, go to labels.fda.gov or call (insert toll-free telephone number) for a faxed, emailed, or mailed copy. In order to ensure that it is readable, the statement would be no smaller than 6-point type. If the

immediate container label is too small to accommodate the statement, the statement must be affixed to the immediate container by other means, such as a peel-back label.

We request comment on the feasibility of requiring a statement of this length on containers such as small volume single dose vials and syringes of product, some of which already bear one or more peel-off labels for product identification and inclusion in patient charts. In addition, we request comments on whether the new required statement will diminish the ability to include peel offs for inclusion in patient charts.

In order to ensure that the prescribing information is accessible in situations when Internet access is not available to the health care professional seeking the current prescribing information, the manufacturer or applicant would be required to print a toll-free telephone number in the statement appearing on the immediate container label and outer container or package that the health care professional could call to have the manufacturer or applicant send the most current prescribing information by FAX, email, or mail. This is intended primarily for use by health care professionals without regular access to the Internet, but could also be used in the case of a public health emergency or natural disaster to the extent that the emergency responders retain some means of communication, *e.g.*, telephone and fax. As discussed in section I.C.3, we expect that in most emergency situations, first responders and other deployed units would be prepared with the key information from prescribing information necessary to appropriately dispense medications in an emergency, even if Internet and other methods of communication are unavailable.

Under proposed § 201.100(c)(5), the manufacturer or applicant would be required to ensure that the toll-free telephone number is current, fully functioning, and maintained so that there is always an alternate method to obtain the current prescribing information if the requestor cannot access the FDA’s labeling repository Web site. The toll-free telephone number service would be required to be available 24 hours a day, 7 days a week. If a request is received for a FAX, email, or mailing of the current prescribing information, the manufacturer or applicant would be required to take adequate steps to ensure that it provides the requested prescribing information promptly. As previously noted, the requirements of this regulation, including the requirement to provide the toll-free number and to provide the

requested prescribing information applies to all manufacturers, including repackagers and relabelers. Thus, each manufacturer would be required to provide a toll-free number on the label and outer container and to respond to requests for faxed, emailed, or mailed copies of the labeling. FDA invites comment on whether these alternatives available on request through the telephone are sufficient methods for obtaining the current prescribing information if it cannot be accessed using the Internet. FDA also invites comment on what would be considered a reasonable amount of time to respond to a request for current prescribing information. The proposed requirement is to “promptly” respond.

C. Paper Versus Electronic

Under proposed § 201.100(c)(3), the covered prescribing information would be distributed electronically and would not be distributed in paper form, except where a paper copy is requested or where an exemption is granted. By contrast, FDA-approved patient package inserts, including patient instructions for use, Medication Guides required under 21 CFR part 208, and any other type of patient labeling are not within the scope of this rule and would continue to be provided in paper form.

The Web site labels.fda.gov presently holds prescribing information submitted to the Agency under current requirements, such as with listing information and annual reports. It is searchable by proprietary name, active ingredient, company name, NDC number, and application number or regulatory citation. We note that certain classes of products, such as cord blood products, may not have a proprietary name or NDC number, and we request comment on other categories by which the repository should be searchable. FDA also solicits comment regarding the ease of use of the labels.fda.gov Web site.

D. Exemptions

Under proposed § 201.100(g) a manufacturer or applicant would be able to submit a written request to FDA for exemption of a human prescription drug from the requirements for electronic distribution of prescribing information. The person requesting the exemption would be required to describe the reasons that compliance with the electronic distribution of prescribing information requirements could adversely affect the safety, effectiveness, purity, or potency of the drug; is not technologically feasible; or is otherwise inappropriate; and explain why the concerns underlying the

request could not reasonably be addressed by other measures. Additionally, FDA, on its own initiative, would be able to exempt a drug from the requirements for electronic distribution of prescribing information, if FDA determines that 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. Examples of circumstances where it may be appropriate to exempt a product from the requirements for electronic distribution of prescribing information include a product which requires multiple steps for reconstitution, a product that is intended for use in an emergency room, or a product that may be stockpiled for use during an emergency. In addition, many cell therapy products require proper handling, preparation, and administration of the final licensed product to ensure that the correct product has been received; that the product remains viable, pure, and potent; and that the product is administered safely. Because steps for ensuring the safety and effectiveness of cell therapy products are important, we request comment on the feasibility of the application of electronic distribution of prescribing information under this proposed rule for cellular therapy products regulated under section 351 of the PHS Act.

We propose that requests for exemption be directed to the appropriate review division and submitted to the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the addresses in proposed § 201.100(g)(2). We plan to issue guidance prior to the effective date of the final regulation to inform manufacturers of any additional means of submitting requests for exemption, such as electronic submission.

E. Submission of Most Current Version of Prescribing Information to FDA

This proposed rule would require submission of the prescribing information, in a format that FDA can process, review, and archive, for distribution via FDA's labeling repository Web site. For newly approved drugs, proposed § 201.100(c)(4) would require that applicants, including NDA, BLA, and ANDA applicants, submit prescribing information in this format in time for the prescribing information to be posted in the labeling repository before the drug enters interstate commerce. For drugs already approved, proposed

§ 201.100(c)(4) would require applicants or manufacturers to submit the most current labeling to FDA each time the prescribing information is changed, including those changes submitted as supplements or in an annual report (§§ 314.70 and 601.12). Compliance with this proposed section would not exempt applicants from compliance with § 314.70 or § 601.12, related to supplements and other changes to approved applications, including for labeling. Applicants would be required to submit updated labeling within 2 business days of FDA approval of a prior approval supplement. Under the proposed regulation, labeling should be submitted to FDA for distribution on the same day that a CBE supplement is submitted to the Agency under § 314.70(c)(6). Manufacturers who are not applicants, for example, repackers, would be required to submit the prescribing information within 2 business days of the posting of the applicant's updated labeling. For unapproved drugs, the person responsible for the content of labeling must submit the labeling within 2 business days of a change to the labeling. Finally, with regard to supplements to ANDAs, we request comment on whether a conforming amendment cross-referencing § 201.100 should be added to § 314.97, which addresses the requirements for submitting supplemental applications and other changes to an approved abbreviated application.

A primary reason for migrating to electronic prescribing information is to ensure that the most up-to-date information about the drug product is available. Currently, per § 207.30(a), every manufacturer required to list drugs under § 207.20 must review and provide updated listing information to the Agency, including labeling, each subsequent June and December, or at their discretion as the change occurs. To minimize the number of submissions to the Agency, if a supplemental change to the prescribing information is submitted to FDA under proposed § 201.100(c)(4) before the required submission for updating electronic registration and listing (part 207), and there is no additional change to the labeling between the time of the § 201.100(c)(4) submission reflecting the supplemental change and the date on which updated drug listing information would be required to be submitted under § 207.30, then this labeling information would not need to be submitted again when electronic registration and listing information is updated.

FDA anticipates that prescribing information will be posted on the next

business day following the date of submission. In addition, under proposed § 201.100(c)(4), it would be the responsibility of the entity who submits the labeling to verify, within 2 business days of submission to the FDA labeling repository, that the correct version of the prescribing information is being distributed at FDA's labeling repository Web site and available for public access. FDA would not be responsible for incorrect prescribing information that is submitted and then posted. If prescribing information is not posted to the labeling repository within 2 business days of submission, the manufacturer, applicant, or other person submitting the labeling must notify FDA's SPL Coordinator by calling 1-888-463-6332 or emailing spl@fda.hhs.gov within 4 business days of submission. If the manufacturer, applicant, or other person submitting the labeling observes that incorrect prescribing information has been posted on the labeling repository, that person must contact FDA's SPL Coordinator by calling 1-888-463-6332 or emailing spl@fda.hhs.gov within 2 business days of its posting. We invite comment on whether this is a sufficient amount of time for a manufacturer or applicant to check the accuracy and completeness of the posted prescribing information. The SPL coordinator should be provided information such as the NDC code, drug name, and a description of the problem with the labeling. If updates to labeling are not provided as required, labeling posted on FDA's labeling repository Web site will be outdated and inaccurate. Outdated labeling posted on the labeling repository renders a product misbranded and in these cases the applicant or manufacturer may be subject to enforcement action by the Agency.

F. Conforming Amendments

We propose the following conforming amendments. Proposed § 201.100(b)(7), would replace the phrase on or within the package from which it is to be dispensed with the phrase either on or within the package from which it is to be dispensed or accompanying the package from which it is to be dispensed under 21 CFR 201.100(b)(8). Proposed §§ 201.100(c)(1) and (d)(2), 201.306(a)(1)(ii) and (b)(2), and 201.310(a) would replace the phrase on or within the package from which the drug is to be dispensed with the phrase either on or within the package from which the drug is to be dispensed or accompanying the package from which the drug is to be dispensed under 21 CFR 201.100(b)(8). The first sentence of § 201.100(d) would be revised to state

whether or not it is on or within a package from which it is to be dispensed or accompanying a package from which the drug is to be dispensed under 21 CFR 201.100(b)(8).

Proposed § 201.100(d)(4) would require that promotional labeling continue to be disseminated with a copy of FDA-approved product labeling in paper form. This requirement would ensure that, for example, a health care professional that receives promotional labeling or detailing materials containing promotional claims would also have the full FDA-approved product labeling readily available in paper form.

The introductory paragraph of § 606.122 would be revised to replace the phrase must be available for distribution with the phrase must be distributed electronically. Finally, paragraph (k) of § 610.61 would be revised to state that the route of administration recommended, or reference to such directions in an enclosed circular or the electronic prescribing information and paragraph (n) would be revised to state that the inactive ingredients when a safety factor, or reference to an enclosed circular or the electronic prescribing information.

V. Legal Authority

FDA is authorized under various sections of the FD&C Act to require that prescribing information be distributed electronically and to require that paper copies of the prescribing information no longer be distributed, except as provided in this regulation, to ensure that human prescription drugs have adequate directions for use and to ensure the efficient enforcement of the FD&C Act. These sections include sections 201(n), 502, 503, 505, and 701(a) of the FD&C Act (21 U.S.C. 321(n), 352, 353, 355, and 371(a)), and section 351 of the PHS Act (42 U.S.C. 262). The electronic distribution of prescribing information for human prescription drugs would permit the efficient enforcement of the misbranding provisions in sections 502(a) and (f) of the FD&C Act, as well as the safety and effectiveness provisions of section 505 of the FD&C Act.

First, FDA has the authority to require that the prescribing information be distributed electronically, rather than by the shipment of a paper copy of the prescribing information with each container of a prescription drug. Under section 502(f) of the FD&C Act, a drug or device is deemed to be misbranded unless its labeling bears adequate directions for use, adequate warnings

against use by patients where its use may be dangerous to health, and adequate warnings against unsafe dosage or methods or duration of administration, in such manner and form as are necessary to protect users. (See 21 U.S.C. 352(f).) Adequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended. (See 21 CFR 201.5.) Additionally, section 502(f) of the FD&C Act authorizes FDA to create a regulatory exemption from this requirement.

Under this authority, FDA has issued regulations exempting drugs subject to section 503(b)(1) of the FD&C Act (prescription drugs) from the requirements of section 502(f)(1) of the FD&C Act if certain conditions are met. (See *e.g.*, 26 FR 8389 (September 6, 1961) (final rule amending then § 1.106 (21 CFR 1.106)); see also 17 FR 6818 (July 25, 1952) (final rule amending then § 1.106).) The 1961 amendments to then § 1.106 exempted a drug subject to section 503(b)(1) of the FD&C Act from section 502(f)(1) of the FD&C Act if, among other things, labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, under which professionals licensed by law to administer the drug can use the drug safely and for the purposes for which it is advertised or represented. (See § 1.106(b)(3).) The relevant provision of the exempting regulations is currently codified at § 201.100(c)(1). Section 201.100(c)(1), like its predecessor § 1.106(b)(3), exempts a drug subject to section 503(b)(1) of the FD&C Act from section 502(f)(1) of the FD&C Act if labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, under which professionals licensed by law to administer the drug can use the drug safely and for the purposes for which it is advertised or represented. Subsection (c)(2) provides that, for an article subject to section 505 of the FD&C Act, the labeling bearing such information is the labeling authorized by the approved new drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of insulin or antibiotic drugs. (See § 201.100(c)(2).)

The review in this proposed rule of the language of the exempting regulations shows that, for decades, the mechanism through which the pharmaceutical industry has met the requirement for exempting a prescription drug from section 502(f)(1) of the FD&C Act is the shipment of a

paper copy of the prescribing information with each container of a prescription drug. The statutory language authorizing FDA to create a regulatory exemption from the requirements of section 502(f)(1) of the FD&C Act is broad. We have concluded that nothing in the statutory language mandates that the regulatory exemption can be met only through shipment of a paper copy of the labeling accompanying each container of the drug. Advances in technology now allow for the electronic distribution of labeling, an option that was not feasible at the time FDA initially issued the predecessor to this proposed regulation.

The electronic distribution of prescribing information is expected to advance: (1) The provision of adequate directions for use to persons prescribing, dispensing, and administering the drug; (2) the provision of adequate warnings to prescribers against use in patients where a drug's use may be dangerous to health; and (3) the prevention of unsafe prescribing of prescription drugs. Currently, the prescriber, health care provider, or pharmacist may review a paper copy of the labeling that has been shipped and stored with a drug for a number of months and that may not contain the most recent information with regard to indications, warnings, or directions for use. In contrast, the electronic distribution of prescribing information provides access to the most recent information about the directions for use, warnings, and contraindications. This information will be available within days of a change via posting on the FDA labeling repository or by FAX, email, or mail. Accordingly, FDA has concluded that it has the authority to amend § 201.100(c)(1) to require that the exemption from section 502(f)(1) of the FD&C Act must be met through electronic means.

Second, FDA concludes that it has authority to base the regulatory exemption from the adequate directions for use requirements of section 502(f) of the FD&C Act on the condition that a paper copy of the prescribing information not be shipped with each container of the drug, except where FDA has concluded that compliance with electronic distribution would adversely affect the safety, effectiveness, purity, or potency of the drug; is not technically feasible; or is otherwise inappropriate. Although the regulation exempting prescription drugs from the requirement to provide adequate directions for use has previously conditioned the exemption on distribution of paper copies of the prescribing information, at the time those regulations were drafted

the electronic distribution of prescribing information was not feasible. As described in this document, given the shelf life of many prescription drug products, changes to the prescribing information may occur between the time a product is shipped from the manufacturer and the time the product is received at the pharmacy or health care facility. Changes to the prescribing information may also occur during the time that the drug is stored at the pharmacy and prior to the time it is dispensed. Under such circumstances, a pharmacist or health care provider who relies upon a paper copy of the labeling, rather than the electronic version, may not have access to the current version of the prescribing information, including the latest warnings or contraindications that may appear in the electronic version of the prescribing information at the time a drug is prescribed and dispensed. Thus, where the electronic distribution of labeling is feasible, the continued distribution of paper labeling is not always sufficient to ensure that the products have adequate directions for use, adequate warnings against use by patients where its use may be dangerous to health, and adequate warnings against unsafe dosage or methods or duration of administration, in such manner and form as are necessary to protect users.

In contrast, the electronic distribution of prescribing information would make it easier for the person prescribing, dispensing, or administering the drug to have full access to all of the drug's current prescribing information, including directions for use, warnings, and contraindications. Specifically, the electronic distribution of the prescribing information via its placement in the FDA labeling repository, accessible through FDA's Web site, would better ensure that pharmacists and other health professionals have access to the most recent version of the directions for use and to the most current warnings and contraindications. With the electronic distribution of prescribing information, pharmacists and health care professionals would have timely access to the most current version of the prescribing information, in contrast to the paper form of the prescribing information, which may contain outdated information by the time it reaches the pharmacist or other health care professional. For these reasons, FDA has concluded that it has legal authority to require the prescribing information no longer physically accompany the product in paper form, except as provided in the exempting provisions of this proposed regulation.

Third, we conclude that FDA has the legal authority to require the label to bear a statement including the FDA labeling repository Web site where the electronic prescribing information will appear and a toll-free telephone number maintained by the manufacturer or applicant and that a manufacturer or applicant must maintain a toll-free telephone number through which individuals may request the prescribing information to be faxed, emailed, or mailed.

As explained in this document, section 502(f) of the FD&C Act provides that a drug is misbranded unless its labeling bears adequate directions for use, adequate warnings against use by patients for whom use may be dangerous to health, and adequate warnings against unsafe dosage or methods or duration of administration in such manner and form as necessary to protect users. Since this rule would make the distribution of this information electronic, the requirement that the Internet address and telephone number appear on the label is necessary so that a health care professional prescribing, administering, or dispensing the product would have the information needed to access the most current prescribing information. This statement will ensure that health care providers are directed to the FDA labeling repository (which will contain the most updated version of the prescribing information), as opposed to other electronic versions of the prescribing information, which may not be updated as frequently as the FDA labeling repository. Similarly, the toll-free number and the requirement that manufacturers and applicants maintain labeling via FAX, email, or mail will ensure that health care providers and pharmacists without Internet access can obtain the most current version of the prescribing information. Thus, this requirement ensures that the prescribing information bearing adequate directions for use, adequate warnings against use by patients for whom use may be dangerous to health, and adequate warnings against unsafe dosage or methods or duration of administration in such manner and form as necessary to protect users accompanies the drug.

In addition, section 502(a) of the FD&C Act prohibits false or misleading labeling of drugs, including the failure to reveal material facts relating to potential consequences under customary conditions of use under section 201(n) of the FD&C Act. The requirement that the label include the Internet address of the FDA labeling repository and the manufacturer's or applicant's telephone number ensures

that the drug product will have accompanying labeling, which should include relevant information such as the drug strength, dosage form, route of administration, active ingredient, and drug interactions. In addition, it ensures that the prescribing information is accurate, up-to-date, and readily available to the health care provider. Because the labeling that is linked to the drug product via either the Internet address or the telephone number includes material facts relating to potential consequences under customary conditions of use under section 201(n) of the FD&C Act, the requirement that the Internet address and telephone number be placed on the label is also justified under section 502(a) of the FD&C Act. Furthermore, section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

For all these reasons, FDA concludes that we have the legal authority to require that the prescribing information be provided electronically, rather than by the shipment of a paper copy of the prescribing information with each container of a prescription drug (except where exempted by this regulation), and to require that the label bear a statement including the Internet address where the electronic labeling may be found and a toll-free telephone number through which individuals may request the prescribing information by other means (such as by FAX, email, or mailing of a paper copy).

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(i) and (k) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection are given under this section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper

performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products

Description: 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.

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.

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, which expires on January 31, 2017). 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 ($1,395 \times 1.25 = 1,744$).

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 ($[200 \times 5.5] \times 1.25 = 1,375$).

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 ($882 \times 1.25 = 1,103$).

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 ($1,830 \times 1.25 = 2,288$).

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 ($2,762 \times 1.25 = 3,453$).

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 ($1,300 \times 1.25 = 1,625$).

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 ($1,300 \times 1.25 = 1,625$) (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 ($3,550 \times 14.60 \times 5 = 259,150$) (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 $[(1,395 + 1,100 + 1,830 + 882 + 2,762 = 7,969) \times 5 = 39,845]$ (table 1). The annual burden of checking the circular of information for accuracy is estimated to be 6,500 $(1,300 \times 5 = 6,500)$. 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 $(3,550 \times 49.3 \times 24 = 4,200,360)$ (table 3).

In addition, immediate container labels and outside packages for newly approved products would need to be designed to include the statement. Because the inclusion of the statement would be one requirement of multiple requirements considered in preparing drug product labels, this burden is included as part of the overall burden to design, test, and produce the label for a drug product's immediate container and outer container or package. The format and content of prescription drug and biological product labels must comply with FDA regulations in 21 CFR part 201 for drugs, including § 201.100(b) and other sections in subparts A and B, and 21 CFR part 610 subpart G. For blood and blood components, the label must comply with 21 CFR part 606 subpart G. Based on characteristics of the product, there are some differences in the label requirements for prescription drugs, biological products and blood and blood components. However, in general, prescription drug labels contain the following information about the drug: (1) Proprietary and established name (or proper name for biological products); (2) recommended or usual dose; (3) route of administration; (4) any warnings or cautionary statements; (5) "Rx only" statement; (6) other required statements or information based on type of product; (7) quantity or proportion of each active ingredient, or amount of product; (8) names of inactive ingredients (if the drug is for other than oral use); (9) identifying lot or control number; (10) manufacturer name and address (and license number for biologics); (11) expiration date; and (12) barcode. Based on FDA's burden estimates for other types of drug product labeling and information from the pharmaceutical industry, FDA estimates that it takes applicants or manufacturers approximately 160 hours to design, test

(i.e., to ensure that the designed label fits on the drug product container or carton), and produce each prescription drug product label, including the statement required under proposed § 201.100(b)(8). Based on an average of the estimated number of SKUs (175,015) and the estimated number of respondents (3,550), as discussed previously, the total burden for the design, testing, and production of prescription drug product labels for existing products is approximately 28,002,400 hours (table 3). Going forward for newly approved drug products, we estimate that the total burden hours for the design, testing and production of new prescription drug product labels for a drug product's immediate container and outer container or package would be approximately 223,220 hours (table 4). This is based on the average annual submission of approximately 150 NDAs from approximately 106 applicants, approximately 1200 ANDAs from approximately 250 applicants, and approximately 45 BLAs from approximately 25 applicants.

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.

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	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Submission of updated labeling and circular of information under § 201.100(c)(4)	3,732	2.5	9,269	1.25	11,586
Review of accuracy of posted labeling and circular of information under § 201.100(c)(4)	3,732	2.5	9,269	5	46,345
Requests for exemptions under § 201.100(g)	10	1	10	1	10
Requests to receive prescribing information by fax, email, or mail when requested (§§ 201.100(c)(5) and 201.100(g))	129,090	1	129,090	*0.25	516,360

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN ^{1 2}—Continued

Type of reporting and 21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
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.

* (15 minutes).

TABLE 2—ESTIMATED ONE-TIME REPORTING BURDEN ¹

Type of reporting and 21 CFR section	Number of respondents	Number 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

Type of disclosure and 21 CFR section	Number of respondents	Frequency per disclosure	Total disclosures	Hours per disclosure	Total hours
Design, testing, and production of labels for existing products	3,550	49.3	175,015	160	28,002,400
Production of new label statement on immediate container label or outside package (Web site and toll-free number) under §§ 201.100(b)(8), 606.121(c)(8)(ii), 610.60(a)(8), and 610.61(t)	3,550	49.3	175,015	24	4,200,360
Total					32,202,760

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

TABLE 4—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN

Type of disclosure and 21 CFR section	Number of disclosures per respondent	Number of responses per respondent	Total annual disclosures	Average burden per disclosure	Total hours	Total capital, operating 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.
Design, testing and production of labels for new prescription drug and biological products and blood and blood components.	381	3.80	1,395	160	223,200	
Total					352,290	

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).

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507)(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. To ensure that comments on the information collection are received by January 20, 2015, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to oira_submission@omb.eop.gov. All comments should be identified with the title "Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products."

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule, does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C.

601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This proposed rule would be an economically significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The proposed rule would have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA expects this proposed rule to result in a 1-year expenditure that would meet or exceed this amount.

Summary

The proposed rule would generate costs to set up a system for the electronic distribution of prescribing information for human prescription drugs. While this system may support

other or all components of the product labeling in addition to the prescribing information, this proposed rule covers the prescribing information portion of product labeling.

The proposed rule would generate costs for users of prescribing information who would need additional hardware, training, Internet access, and information access time. In addition, incremental costs would be associated with some printing of the prescribing information. Table 5 shows a summary of the ranges of annualized costs using discount rates of 7 percent and 3 percent over 10 years. The proposed rule would generate benefits in the form of production cost savings because eliminating the production of most paper forms would reduce the costs of providing prescribing information on human prescription drugs. Table 5 shows the ranges of savings. The large ranges for both costs and savings indicate the uncertainty associated with such a large change in practices for such a large number of manufacturers and users. If we use a 7 percent discount rate to annualize the costs and savings over 10 years, the effects of the proposed rule could range from annualized net savings of \$5.0 million to annualized net savings of \$73.5 million. With a 3 percent discount rate to annualize cost savings, the effects could range from an annualized net savings of \$10.0 million to annualized net savings of \$82.2 million. These quantified effects do not include the public health benefits associated with users having access to the most up-to-date versions of the prescribing information.

The full assessment of the economic analysis is available in Docket FDA-2007-N-0363 and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm> (Ref. 7).

TABLE 5—SUMMARY OF ANNUALIZED COSTS AND COST SAVINGS
[In millions]

	Low (7%)	High (7%)	Low (3%)	High (3%)
Cost Savings	\$51.8	\$163.7	\$56.6	\$170.8
Costs	46.8	89.2	46.6	88.6
Net Savings (Cost Savings – Costs)	5.0	73.5	10.0	82.2

X. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of

comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and

will be posted to the docket at <http://www.regulations.gov>.

XI. Proposed Effective Date

We propose that any final rule based on this proposal become effective 6 months after publication in the Federal Register. Implementation of this rule

would require that manufacturers and applicants have up-to-date electronic prescribing information posted on FDA's labeling repository Web site, that manufacturers and applicants have verified the content of that information, that the immediate container label and outer container or package bear the required statement, and that paper labeling no longer accompany the drug. The FDA labeling repository Web site is currently available at labels.fda.gov and is populated with prescribing information submitted to the Agency under current regulatory requirements, such as requirements to submit labeling with listing information or with annual reports. If the prescribing information available in the repository is current, manufacturers and applicants would not be required to resubmit labeling before beginning the electronic distribution of labeling.

Any human prescription drug that an applicant or manufacturer introduces into interstate commerce after the effective date that does not have accurate, complete, and updated electronic prescribing information available on FDA's labeling repository Web site, as well as the statement on the product's immediate container label and the outer container or package explaining how to access the information, or that continues to be accompanied by paper prescribing information would not meet the criteria to be exempt from the requirement to provide "adequate directions for use" and would be misbranded under section 502(f)(1) of the FD&C Act. As explained further in section XII, we understand that 6 months is not likely to be sufficient time for many manufacturers and applicants to implement this rule with regard to some or all of their marketed products. As a result, we are proposing to exercise enforcement discretion for 2 years from publication of the final rule. However, we anticipate that some will be able to comply with the rule beginning on the effective date. We want to ensure that those that are able to comply as soon as 6 months after publication can take advantage of the benefits of electronic distribution of labeling at that time and will no longer need to provide paper labeling with their products (as long as all other requirements of the rule are met). Because, technically, full implementation (elimination of paper labeling that accompanies the product) cannot take place until the rule is effective, a longer effective date could delay implementation by those able to comply as soon as 6 months after the publication date. We request comment

on whether a 6 month effective date is sufficient given the concerns raised in the GAO report about potential workflow disruptions in pharmacies as a result of an online-only system for prescribing information. Additionally, FDA requests comments on whether a dual system, where the regulation would require distribution of both paper and electronic versions of labeling until the compliance date, is desirable and information about the potential benefits or consequences of such a requirement.

XII. Proposed Compliance Date

Given the time that may be needed for industry to make necessary changes to the drugs' immediate container labels and outer containers or packages to comply with this rule and to enable firms to exhaust existing stock of drugs already packaged with paper prescribing information, we propose a compliance date of 2 years after the final rule is published. Thus, until the compliance date, we will exercise enforcement discretion with regard to products subject to the electronic labeling requirements, so long as those products continue to be distributed with the current prescribing information in paper form. However, a product distributed between the effective date and the compliance date that bears the new required statement on the label and outer container must have the current electronic prescribing information in the labeling repository at labels.fda.gov and should not be accompanied by the paper prescribing information.

We note that registration and listing information for blood and blood components is currently not electronically submitted to the Agency. FDA is in the process of developing standards for the electronic submission of labeling for blood and blood components. The Agency will consider progress in developing such standards when setting a compliance date in a final rule for blood and blood components and/or on our own initiative grant an exemption for blood and blood components for a period of time until electronic submission of the labeling for blood and blood components is supported. Thus, the final regulation may include staggered compliance dates, with a later compliance date for blood and blood components and an earlier compliance date for all other drug products.

FDA is requesting comments on the proposed effective and compliance dates, and whether they are appropriate. Specifically, we request comment on whether a delayed compliance date would alleviate concerns raised in the GAO report about potential workflow

disruptions in pharmacies as a result of an online-only system for prescribing information and, if so, how much additional time would be needed to change operations.

XIII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site address in this reference section, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. "Electronic Drug Labeling: No Consensus on the Advantages and Disadvantages of Its Exclusive Use," GAO-13-592, Report by the Government Accountability Office, July 8, 2013.
2. "Analysis of the Feasibility of Safety Labeling Changes Implementation Timeline," Final Report by Eastern Research Group, Inc., June 22, 2012.
3. Ho, Y., Q. Chen, H. Nian, K.B. Johnson, "An Assessment of Pharmacists' Readiness for Paperless Labeling: A National Survey," *Journal of the American Medical Informatics Association*, 1-6, 2013.
4. Internal analysis of safety-related labeling changes approved by FDA between 2003 and 2013.
5. Internal review of labeling changes for new molecular entities for calendar years 2005 to 2007.
6. "Electronic Distribution of Labeling Proposed Rule Final Report Economic Impact Analysis," Report by Eastern Research Group, Inc., October 4, 2010.
7. Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products; Proposed Rule, available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public

Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201, 606, and 610 be amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Amend § 201.100 as follows:

■ a. In paragraph (b)(7), remove the phrase “on or within the package from which it is to be dispensed” and add in its place “either on or within the package from which it is to be dispensed, or accompanying the package from which it is to be dispensed under paragraph (b)(8) of this section”;

■ b. Add paragraph (b)(8);

■ c. In paragraph (c)(1) remove the phrase “on or within the package from which the drug is to be dispensed” and add in its place “on or within or accompanying the package from which the drug is to be dispensed under paragraph (b)(8) of this section”;

■ d. Add paragraphs (c)(3) through (5);

■ e. Revise the introductory text of paragraph (d);

■ f. In paragraph (d)(2), remove the phrase “on or within the package from which the drug is to be dispensed” and add in its place “on or within or accompanying the package from which the drug is to be dispensed under paragraph (b)(8) of this section”;

■ g. Add paragraphs (d)(4) and (g).

The additions and revisions read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(b) * * *

(8) The statement: “To obtain the current prescribing information, go to *labels.fda.gov* or call (insert the toll-free telephone number) for a faxed, emailed, or mailed copy.” This statement must be no smaller than 6-point type. *Provided, however,* that in the case of a container too small or otherwise unable to accommodate a label with sufficient space to bear the statement, the statement shall be affixed to the immediate container label by other means, such as a peel-back label. *Additionally,* if the container is packaged within an outer container from which it is removed for dispensing or use, the statement shall also be included on the outer container or package.

(c) * * *

(3) Labeling containing prescribing information accompanying the package from which the drug is to be dispensed under paragraphs (b)(8) and (c)(4) of this section is distributed electronically and not in paper form except for any FDA-approved patient labeling, any labeling containing prescribing information that is distributed upon request by FAX or mail, any labeling distributed under the exemption provisions of paragraph (g) of this section that is on or within the package from which the drug is to be dispensed, and any prescribing information accompanying promotional labeling.

(4) Labeling containing prescribing information must be submitted to FDA in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Upon initial approval of a new drug or biological product, labeling containing prescribing information must be submitted and posted before introducing the drug into interstate commerce. For drugs already approved under section 505 of the Federal Food, Drug, and Cosmetic Act or biological products licensed under section 351 of the Public Health Service Act, applicants must submit labeling containing prescribing information within 2 business days of a change to the prescribing information. For unapproved drugs, the person responsible for the content of labeling must submit labeling containing prescribing information within 2 business days of the posting or new posting of an applicant's labeling. The entity responsible for submitting the labeling for the drug must verify that the correct version of the prescribing information appears on FDA's labeling repository Web site *labels.fda.gov*. The entity responsible for submitting the labeling must contact FDA's Structured Product Labeling Coordinator by calling 1-888-463-6332 or emailing *spl@fda.hhs.gov* within 4 business days of its submission if the labeling is not posted on FDA's labeling repository Web site or within 2 business days of its posting if the labeling that is posted is incorrect. Products with missing, inaccurate, false, misleading, or outdated labeling on the FDA's labeling repository Web site are misbranded.

(5) The applicant, manufacturer, or person responsible for the content of

labeling must provide a toll-free telephone number in the label statement required in paragraph (b)(8) of this section.

(i) The applicant, manufacturer, or person responsible for the content of labeling must ensure that the telephone number is current, fully functioning, and maintained for 24 hours a day, 7 days a week.

(ii) The applicant, manufacturer, or person responsible for the content of labeling must have a fully functioning and maintained system to respond to requests to obtain an alternate form of the prescribing information which the manufacturer receives through the toll-free number. The applicant, manufacturer, or person responsible for the content of labeling must take adequate steps to provide the requested prescribing information promptly to the requestor.

(d) Any labeling, as defined in section 201(m) of the Federal Food, Drug, and Cosmetic Act, whether or not it is on or within a package from which the drug is to be dispensed or accompanying a package from which the drug is to be dispensed under paragraph (b)(8) of this section, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.105(b)(2)) contains:

* * * * *

(4) In the case of prescribing information accompanying promotional labeling, the information required, in paper form and in the format specified, by §§ 201.56, 201.57, and 201.80.

* * * * *

(g) If FDA has granted an exemption of the drug from the requirements for the electronic distribution of labeling, the applicant, manufacturer, or person responsible for the content of labeling of unapproved drugs, distributes the content of labeling in paper form.

(1) On FDA's initiative, or in response to a written request from an applicant, manufacturer, or person responsible for the content of labeling of unapproved drugs, the appropriate Center Director may exempt a human prescription drug 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 explain why the concerns underlying the request could not reasonably be addressed by other measures. If an exemption is granted, the applicant, manufacturer, or person responsible for the content of labeling of unapproved drugs must distribute the content of labeling in paper form.

(2) For products regulated by the Center for Drug Evaluation and Research, requests for an exemption should be sent to the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, or for drug products for which there is no reference listed drug, to the Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. For products regulated by the Center for Biologics Evaluation and Research, requests for an exemption should be submitted to the attention of the appropriate Review Division in the relevant Center for Biologics Evaluation and Research Product Office using the following address: Center for Biologics Evaluation and Research, Food and Drug Administration, Document Control Center, 1401 Rockville Pike (HFM-99), Rockville, MD 20852.

■ 3. In § 201.306, revise paragraph (a)(1)(ii) introductory text and paragraph (b)(2) to read as follows:

§ 201.306 Potassium salt preparations intended for oral ingestion by man.

(a) * * *

(1) * * *

(ii) The labeling either on or within the package from which the drug is to be dispensed or accompanying the package from which the drug is to be dispensed under § 201.100(b)(8) bears adequate information for its use by practitioners in accord with the “full disclosure” labeling requirements of § 201.100, including the following warning statement: * * *

* * * * *

(b) * * *

(2) The labeling either on or within the package from which the drug is to be dispensed or accompanying the package from which the drug is to be dispensed under § 201.100(b)(8) bears adequate information for its use by practitioners in accord with the “full disclosure” labeling requirements of § 201.100, including a recommendation that patients be directed to dissolve any such tablets in an appropriate amount of liquid and to dilute any such liquid preparations adequately to assure against gastrointestinal injury associated

with the oral ingestion of concentrated potassium salt preparations.

■ 4. In § 201.310, revise the third sentence of paragraph (a) to read as follows:

§ 201.310 Phenindione; labeling of drug preparations intended for use by man.

(a) * * * In view of the potentially serious effects found to be associated with preparations of this drug intended for use by man, the Commissioner of Food and Drugs will regard such preparations as misbranded within the meaning of section 502(f)(1) and (2) of the Federal Food, Drug, and Cosmetic Act, unless the label and labeling either on or within the package from which the drug is to be dispensed or accompanying the package from which the drug is to be dispensed under § 201.100(b)(8), and any other labeling furnishing or purporting to furnish information for use of the drug, bear a conspicuous warning statement to the following effect: * * *

* * * * *

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

■ 5. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 6. In § 606.121 revise paragraph (c)(8)(ii) to read as follows:

§ 606.121 Container label.

* * * * *

(c) * * *

(8) * * *

(ii) “See circular of information for indications, contraindications, cautions, and methods of infusion. To obtain the current circular of information, go to *labels.fda.gov*, or call (insert toll-free telephone number) for a faxed, emailed, or mailed copy.” This statement must be no smaller than 6-point type.

* * * * *

§ 606.122 [Amended]

■ 7. In § 606.122 introductory text, remove the words “must be available for distribution” and add in their place “must be distributed electronically.”

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

■ 8. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

■ 9. In § 610.60, add paragraph (a)(8) to read as follows:

§ 610.60 Container label.

(a) * * *

(8) The container label for biological products must bear the statement: “To obtain the current prescribing information, go to *labels.fda.gov*, or call (insert the toll-free telephone number) for a faxed, emailed, or mailed copy.” This statement must be no smaller than 6-point type. If the container label is incapable of bearing the statement due to inadequate space, the statement must be affixed to the container by other means, such as a peel-back label.

* * * * *

■ 10. In § 610.61, revise paragraphs (k) and (n) and add paragraph (t) to read as follows:

§ 610.61 Package label.

* * * * *

(k) The route of administration recommended, or reference to such directions in an enclosed circular or the electronic prescribing information;

* * * * *

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular or the electronic prescribing information;

* * * * *

(t) The package label for products must bear the statement: “To obtain the current prescribing information, go to *labels.fda.gov* or call (insert the toll-free telephone number) for a faxed, emailed, or mailed copy.” This statement must be no smaller than 6-point type.

Dated: December 11, 2014.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2014–29522 Filed 12–16–14; 11:15 am]

BILLING CODE 4164–01–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[EPA–R05–OAR–2014–0661; FRL–9920–46–Region–5]

Approval and Promulgation of Air Quality Implementation Plans; Indiana; Ozone and PM_{2.5} Standards

AGENCY: Environmental Protection Agency.

ACTION: Proposed rule.

SUMMARY: The Environmental Protection Agency (EPA) is proposing to approve a submission by the State of Indiana as a revision to the Indiana State Implementation Plan (SIP). The