

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 201, 208, 314, 606, and 610**

[Docket No. FDA-2019-N-5959]

RIN 0910-AH68

Medication Guides: Patient Medication Information**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its human prescription drug product labeling regulations for Medication Guides (FDA-approved written prescription drug product information distributed to patients). This action, if finalized, will require applicants to create a new type of Medication Guide, referred to as Patient Medication Information (PMI), for prescription drug products, including biological products, used, dispensed, or administered on an outpatient basis and for blood and blood components transfused in an outpatient setting. PMI would be a one-page document with standardized format and content that would be submitted to FDA for approval. This proposed rule is intended to improve public health by providing patients with clear, concise, accessible, and useful written prescription drug product information delivered in a consistent and easily understood format to help patients use their prescription drug products safely and effectively.

DATES: Either electronic or written comments on the proposed rule must be submitted by November 27, 2023. Submit written comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 by November 27, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 27, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

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

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-N-5959 for "Medication Guides: Patient Medication Information." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- **Confidential Submissions—**To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential

with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://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 Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Submit comments on the information collection under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting "Currently under Review—Open for Public Comments" or by using the search function. The title of this proposed collection is "Medication Guides: Patient Medication Information."

FOR FURTHER INFORMATION CONTACT:

With regard to the proposed rule: Chris Wheeler, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3330, Silver Spring, MD 20993, 301-796-0151, Chris.Wheeler@fda.hhs.gov; or Diane Maloney, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

With regard to the information collection: Domini Bean, Office of

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend its prescription drug product labeling regulations for Medication Guides to require a new type of Medication Guide, referred to as PMI, for prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an outpatient setting. For the purposes of this proposed rule, a prescription drug product also includes a biological product licensed under the Public Health Service Act (PHS Act). Currently, Medication Guides are required only for certain prescription drug products that FDA determines pose a significant and serious public health concern and are used primarily on an outpatient basis.

We have long recognized the importance of providing patients with written information about their prescription drug products because there is evidence that such information may help patients use prescription drug products safely and effectively and may potentially reduce preventable adverse drug reactions and improve health outcomes. Patients may currently receive one or more types of written patient information regarding prescription drug products, including patient package inserts (PPIs), Medication Guides, consumer medication information (CMI), and Instructions for Use documents. This written patient information, in certain instances, has been duplicative, incomplete, conflicting, or difficult to read and understand, and has not been sufficient to meet the needs of patients. PMI is intended to improve public health by providing patients with clear, concise, accessible, and useful written prescription drug product information delivered in a consistent and easily understood format to help patients use their prescription drug products safely and effectively.

B. Summary of the Major Provisions of the Proposed Rule

Under the proposed rule, PMI would highlight essential information that the patient needs to know about the prescription drug product and basic directions on how to use the product. PMI would be a one-page document that follows standardized format and content requirements. PMI would consist of the following headings:

- [Insert Drug Name] is
- Important Safety Information
- Common Side Effects
- Directions for Use

In determining specific headings and information to be included in PMI, we researched scientific literature, conducted studies examining several PMI prototypes, held public workshops and hearings, and obtained stakeholder input on what information patients need in order to use their prescription drug products safely and effectively.

When finalized, this proposed rule would require applicants of all new and approved new drug applications (NDAs) and biologics license applications (BLAs) to create PMI for prescription drug products that are to be used, dispensed, or administered on an outpatient basis. Applicants of NDAs and BLAs would be required to submit PMI to FDA for approval. The proposed rule covers NDAs and BLAs for interchangeable biosimilars and non-interchangeable biosimilars.

When finalized, the proposed rule would also require applicants of new and approved abbreviated new drug applications (ANDAs) that refer to a listed drug for which FDA has approved PMI to have PMI that is the same as that of the reference listed drug (RLD) except for certain differences in labeling permitted under the law. As described further in this document, FDA will create a PMI template for approved NDAs if: (1) the ANDA references a listed drug whose approval has been withdrawn and (2) no PMI was approved for the RLD before the approval of the RLD was withdrawn.

PMI would be stored in an online central repository managed by FDA and would be freely accessible to the public, including patients, healthcare providers, and authorized dispensers.

Authorized dispensers would be required to provide PMI to patients each time a prescription drug product for which an FDA-approved PMI exists is used, dispensed, or administered on an outpatient basis. The default method of distribution for PMI is in paper form. Although authorized dispensers would be required to have paper distribution of PMI available upon request, this proposed rule would allow for electronic distribution instead of paper distribution upon a patient's request and would accommodate future technological advances in the methods used to provide PMI upon a patient's request.

When finalized, this proposed rule would require that PMI be available for distribution to transfusion services of blood and blood components, unless a waiver applies. The requirement to create PMI and make it available for distribution to transfusion services applies to all establishments that collect blood and blood components for

transfusion. However, only licensed blood establishments would be required to submit PMI to FDA for approval. Each time blood or blood components are administered on an outpatient basis, transfusion services would be considered authorized dispensers and would be required to provide PMI to each patient. This approach would ensure that every patient who receives blood or a blood component with an associated PMI on an outpatient basis would receive that PMI.

FDA would withdraw the current regulations requiring Medication Guides for certain prescription drug products after all prescription drug products that currently have Medication Guides have FDA-approved PMI. During the proposed 5-year implementation schedule of the final rule, the current regulations governing Medication Guides would remain in place but would no longer be applicable to a prescription drug product once that prescription drug product has FDA-approved PMI.

FDA would also withdraw the current regulations requiring PPIs for oral contraceptives and estrogen-containing products after all such prescription drug products that had PPIs have FDA-approved PMI. During the proposed 5-year implementation schedule of the final rule, the current regulations for PPIs would remain in place but would no longer be applicable to a prescription drug product once that prescription drug product has FDA-approved PMI. Under this proposed rule, once finalized, we would no longer accept

voluntary submissions of PPIs for prescription drug products.

C. Legal Authority

FDA’s proposed revisions to the format and content requirements for prescription drug labeling are authorized by the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the PHS Act.

D. Costs and Benefits

This proposed rule would require that all human prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an outpatient setting, be accompanied by a one-page product information document, or Medication Guide, known as PMI. The public would benefit from this labeling with decreased search costs for information. The public may also benefit from a reduction in risk associated with their drug products, including blood and blood component products transfused in outpatient settings, due to the availability of PMI if the new labeling helps patients make better healthcare decisions. We estimate that the present discounted value of these potential benefits from PMI over 10 years would range between \$127.5 million and \$4.3 billion using a 3 percent discount rate, with a primary estimate of \$1.6 billion; using a 7 percent discount rate, the present-value benefits from PMI would range between \$101.0 million and \$3.4 billion, with a primary estimate of \$1.3 billion. Annualized over 10 years, we estimate that the benefit from PMI would range

between \$14.9 and \$507.9 million per year, with a primary estimate of \$188.0 million, using a 3 percent discount rate; with a 7 percent discount rate, we estimate the annualized benefit to range between \$14.4 and \$486.8 million, with a primary estimate of \$180.5 million per year. We estimate that annual benefits would be constant beginning in year 5.

The proposed rule would impose costs on industry, the majority of which would stem from developing PMI. The proposed rule would also impose costs on FDA, primarily from reviewing PMI submissions, developing PMI templates for a small subset of drugs, and establishing and maintaining the online PMI database. We estimate that the total present value of net costs over 10 years would range from \$105.0 to \$312.5 million, with a primary estimate of \$192.8 million, using a 3 percent discount rate and from \$89.0 to \$263.6 million, with a primary estimate of \$162.6 million, using a 7 percent discount rate. Annualizing these costs over 10 years, we estimate the cost would range from \$12.3 to \$36.6 million per year at a 3 percent discount rate, with a primary estimate of \$22.6 million per year, and from \$12.7 to \$37.5 million per year using a discount rate of 7 percent, with a primary estimate of \$23.2 million. We estimate that annual costs would be constant beginning in year 5. Dispensers may face additional costs to distribute PMI that we cannot estimate at this time.

II. Table of Abbreviations and Acronyms Commonly Used in This Document

Abbreviation/acronym	What it means
ANDA	Abbreviated New Drug Application.
BLA	Biologics License Application.
CDC	Centers for Disease Control and Prevention.
CMI	Consumer Medication Information.
DESI	Drug Efficacy Study Implementation.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA	Food and Drug Administration.
HHS	Department of Health and Human Services.
NDA	New Drug Application.
NVICP	National Vaccine Injury Compensation Program.
OMB	Office of Management and Budget.
PHS Act	Public Health Service Act.
PI	Prescribing Information.
PMI	Patient Medication Information.
PPI	Patient Package Insert.
RCAC	FDA Risk Communication Advisory Committee.
REMS	Risk Evaluation and Mitigation Strategy.
RLD	Reference Listed Drug.
VISs	Vaccine Information Statements.

III. Background

A. Introduction

Currently, patients may receive one or more types of written patient prescription drug product information in an outpatient setting when they receive a prescription medication, including: (1) PPIs, (2) Medication Guides, (3) CMI, and (4) Instructions for Use documents. Medication Guides and some PPIs are required under the FD&C Act (see section 505–1 of the FD&C Act (21 U.S.C. 355–1)) and FDA regulations (see part 208 (21 CFR part 208)) and §§ 310.501 and 310.515 (21 CFR 310.501 and 310.515)). CMI is produced by voluntary private sector entities and is intended to provide general written patient prescription drug product information to patients. An Instructions for Use document is developed by applicants and is intended for patients who use prescription drug products that have complicated or detailed patient-use instructions.

1. Patient Package Insert (PPI)

A PPI is written prescription drug product information developed by applicants for patients. Current FDA regulations require that applicants develop PPIs for oral contraceptives and estrogen-containing products (see §§ 310.501 and 310.515). Applicants must submit the required PPIs to FDA for approval and provide FDA-approved PPIs with each package of the drug product that the manufacturer or distributor intends to dispense to patients. Applicants can also voluntarily create a PPI for other prescription drug products and may submit it to FDA for approval as part of a prescription drug product's labeling. However, distribution of a voluntarily submitted PPI is not required, even if it is FDA-approved.

FDA can require a risk evaluation and mitigation strategy (REMS) when FDA determines a REMS is necessary to ensure that the benefits of a prescription drug product outweigh the risks (see section 505–1 of the FD&C Act). Under section 505–1(e) of the FD&C Act, PPIs are one potential element of a REMS if FDA determines that a PPI may help mitigate a serious risk of the prescription drug product.¹

2. Medication Guide for Prescription Drug Products

Currently, a Medication Guide is FDA-approved written patient prescription drug product information for certain prescription drug products

that are used primarily on an outpatient basis (see part 208). Under current regulations, FDA requires a Medication Guide when FDA determines one or more of the following circumstances exist: (1) the prescription drug product is one for which patient labeling could help prevent serious adverse effects; (2) the prescription drug product is one that has a serious risk or risks (relative to benefits) of which patients should be made aware, because information concerning the risk or risks could affect a patient's decision to use or continue to use the product; or (3) the prescription drug product is important to health, and patients' adherence to directions for use is crucial to the prescription drug product's effectiveness (§ 208.1(c) (21 CFR 208.1(c))).

FDA can also require Medication Guides as an element of a REMS under section 505–1(e) of the FD&C Act. In the **Federal Register** of November 18, 2011 (76 FR 71577), FDA published a notice of availability of a guidance for industry entitled “Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)” (available at: <https://www.fda.gov/media/79776/download>) to clarify when Medication Guides would be a part of a REMS and to clarify when FDA intended to exercise enforcement discretion regarding when a Medication Guide must be provided to a patient.

Medication Guides contain information that is necessary to a patient's safe and effective use of a prescription drug product. For those selected prescription drug products that currently have Medication Guides, Medication Guides are developed by applicants, approved by FDA, and required to be distributed to patients.

3. Consumer Medication Information (CMI)

CMI is written patient prescription drug product information that is developed by organizations or individuals in the private sector other than the applicant of the prescription drug product. CMI is intended for voluntary distribution to patients when a prescription drug product is dispensed from a pharmacy. CMI is not developed by or in consultation with the applicant, is not approved by FDA, and is not required by FDA to be distributed to patients.

Different organizations and individuals create CMI and make it available to pharmacies for purchase. FDA provides recommendations for creating useful CMI through guidance (available at: <https://www.fda.gov/>

[media/72574/download](https://www.fda.gov/media/72574/download)). However, CMI is not standardized, and the content, even for the same prescription drug product, can vary greatly depending on which organization or individual created the CMI.

4. Instructions for Use

For certain prescription drug products that have complicated or detailed patient-use instructions, applicants may develop an Instructions for Use document. The Instructions for Use document, if developed, is reviewed and approved by FDA and is generally provided when the drug is dispensed to the patient. In the **Federal Register** of July 15, 2022 (87 FR 42485), FDA published a notice of availability of a final guidance for industry entitled “Instructions for Use—Patient Labeling for Human Prescription Drug and Biological Products—Content and Format” (available at: <https://www.fda.gov/media/128446/download>) to provide recommendations for developing the content and format of an Instructions for Use document for human prescription drugs and biological products and drug-device or biologic-device combination products submitted under an NDA or BLA. This guidance represents FDA's current thinking on this topic.

B. Need for the Regulation

We have long recognized the importance of providing written information to patients about their prescription drug products. There is evidence that prescription drug product information may help patients use their prescription drug products safely and effectively, which may reduce preventable adverse drug events and improve health outcomes. For example, written prescription drug product information is an important part of patient counseling because it reinforces verbal instructions or warnings given by healthcare providers, may improve patient understanding and recall of instructions, and provides patients with supplemental information about the prescription drug product after visits with healthcare providers (Ref. 1). We evaluated the current system for written prescription drug product information, which includes Medication Guides, PPIs, CMI, and Instructions for Use. Based on that evaluation (discussed below in detail), we have determined that the current system does not consistently provide patients with clear, concise, accessible, and sufficiently useful written prescription drug product information delivered in a consistent and easily understood format to help patients use their prescription drug

¹ Currently, there are no REMS that contain a PPI as an element.

products safely and effectively.

Therefore, we are proposing a new type of Medication Guide to help patients use their prescription drug products safely and effectively.

In addition, a common major public health problem is that some patients do not adhere to prescription drug therapy (e.g., for antihypertensive drugs), and some patients do not use their prescribed drugs as directed by their healthcare providers (Refs. 2 through 4). Reports show that patients' nonadherence to long-term prescription drug product therapies negatively affects patient outcomes and has led to preventable healthcare costs (Refs. 3 and 5). It is estimated that nonadherence contributes to as many as 25 percent of hospital admissions (Ref. 4), 50 percent of treatment failures, and approximately 125,000 deaths in the United States per year (Refs. 2 and 4).

Although the reasons for medication nonadherence are multidimensional (Ref. 2), patients' knowledge about prescription drug products is important for adherence (Ref. 6). To help increase patients' knowledge, information about prescription drug products should be communicated to patients when these products are dispensed, administered, or used on an outpatient basis (Ref. 2). This information can remind patients about important information regarding the prescription drug product and answer questions that arise after patients have visited a healthcare provider (Ref. 7).

1. Previous Efforts To Provide Written Prescription Drug Product Information to Patients

Since the 1970s, we have required that useful patient prescription drug product labeling written in nontechnical language be distributed to patients every time certain prescription drug products are dispensed. Specifically, we published regulations requiring that manufacturers/distributors of oral contraceptive drug products (see § 310.501; 35 FR 9001, June 11, 1970; and 43 FR 4214, January 31, 1978) and estrogen-containing drug products (see § 310.515 and 42 FR 37636, July 22, 1977) provide patients with PPIs containing information about the prescription drug product's benefits and risks.

In the **Federal Register** of July 6, 1979 (44 FR 40016), we published a proposed rule that would have required written patient information for most prescription drug products in addition to PPI for oral contraceptives and estrogen-containing products. However, in the **Federal Register** of September 12, 1980 (45 FR 60754), the final rule

instead required procedures for preparing and distributing PPIs for a limited number of prescription drug products in addition to PPI for oral contraceptives and estrogen-containing products.

FDA proposed to revoke the final rule in the **Federal Register** of February 17, 1982 ((47 FR 7200) and reprinted February 19, 1982 (47 FR 7458)). In the **Federal Register** of September 7, 1982 (47 FR 39147), we revoked the final rule.

In the **Federal Register** of August 24, 1995 (60 FR 44182), we published a proposed rule entitled "Prescription Drug Product Labeling: Medication Guide Requirements" (1995 proposed rule) (available at: <https://www.govinfo.gov/content/pkg/FR-1995-08-24/pdf/95-21020.pdf>), which was intended to help patients receive useful written information about prescription drug products. If finalized, the 1995 proposed rule would have set specific distribution and quality goals and timeframes for distributing useful written patient information. The proposed rule would have required applicants to prepare and distribute Medication Guides or provide the means to distribute Medication Guides for a limited number of prescription drug products (primarily used on an outpatient basis) that FDA determined posed a serious and significant public health concern requiring the immediate distribution of FDA-approved patient information.

Consistent with the health promotion and disease prevention objectives of Healthy People 2000 (Ref. 8), the 1995 proposed rule would have also set a goal for distributing useful written patient information for those prescription drug products that did not require Medication Guides. The goal was that the private sector initiatives would result in the distribution of useful written patient information to 75 percent of individuals receiving new prescriptions by 2000 and to 95 percent of individuals receiving new prescriptions by 2006.

The 1995 proposed rule described criteria to determine the usefulness of written patient information. We described useful written patient information as information written in nontechnical language and containing a summary of the most important information about a drug product. We also specified that the usefulness of written patient information would be evaluated based on scientific accuracy, consistency with a standard format, nonpromotional tone and content, specificity, comprehensiveness, understandable language, and legibility.

If the 1995 proposed rule had been finalized, we would have periodically evaluated and reported on the private sector's progress towards achieving the target goals. If the goals were not met in the specified timeframes, we proposed that we would either implement a mandatory comprehensive Medication Guide program or seek public comments on whether a comprehensive program should be implemented. Additionally, we would try to determine whether any other steps were needed to meet the goals of patient prescription drug product information.

As we were reviewing the public comments to the 1995 proposed rule, Congress enacted Public Law 104-180 (the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 1997) on August 6, 1996. A goal of section 601(b) of Public Law 104-180 was for the private sector to distribute useful written prescription information to 75 percent of individuals receiving new prescriptions by 2000 and to 95 percent of individuals receiving new prescriptions by 2006, consistent with the goals of the 1995 proposed rule. Section 601(a) of the law also required the Secretary of the Department of Health and Human Services (Secretary) (HHS) to organize a committee of interested stakeholders to develop a long-range, comprehensive action plan to achieve this goal.

Section 601(d) of the law prohibited us from taking further regulatory steps at that time to require a uniform content or format for written prescription drug product information that was voluntarily provided to patients if private sector initiatives met the goal within the specified timeframes. FDA was charged with evaluating the private sector's progress in meeting the goal of distributing useful written prescription drug product information beginning January 1, 2001. If, after reviewing the private sector initiatives, FDA determined that the goals of the law had not been met, FDA could seek public comments on alternative initiatives to meet the goal.

In response to the Public Law 104-180 mandate, the Secretary convened a steering committee composed of healthcare professionals, consumer organizations, pharmaceutical manufacturers, prescription drug wholesalers, drug information database companies, CMI developers, and others. The steering committee created a long-term action plan for improving oral and written prescription drug product information, reported in the 1996 "Action Plan for the Provision of Useful Prescription Medicine Information"

(Keystone Action Plan) (Ref. 9). The Keystone Action Plan endorsed the elements specified in Public Law 104–180 for defining the usefulness of prescription drug product information, specifically that the materials should be scientifically accurate, unbiased in content and tone, sufficiently specific and comprehensive, and presented in an understandable and legible format that is readily comprehensible to patients and is timely and up to date. The Keystone Action Plan explained that written prescription drug product information that meets these criteria for usefulness would enable patients to use their prescription drug products properly and appropriately, receive the maximum benefit from the prescription drug products, and avoid harm.

In the **Federal Register** of December 1, 1998 (63 FR 66378), we published a final rule requiring the mandatory distribution of Medication Guides for a small number of prescription drug and biological products that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient medication information. FDA anticipated that on average, no more than 5 to 10 prescription drug products per year would require such information. However, because of the types and characteristics of the prescription drug products approved, the number of prescription drug products required to have Medication Guides has increased significantly to over 550 Medication Guides since publication of the final rule in 1998 (approximately 20 to 25 per year).

2. FDA's Evaluation of the Private Sector's Progress To Provide Written Prescription Drug Product Information to Patients

Consistent with Public Law 104–180, the Keystone Action Plan required the development of mechanisms to periodically assess the quality of written prescription drug product information. We were charged with evaluating the private sector's progress toward meeting the goal of distributing useful written prescription drug product information (Ref. 9). Subsequently, we contracted with the National Association of Boards of Pharmacy and a group of academics to conduct several studies to determine the private sector's progress toward meeting the goal of Public Law 104–180.

In 1999, an initial study assessed the CMI that was voluntarily provided to patients receiving new prescriptions at pharmacies (the 1999 study) (Ref. 1). The 1999 study assessed the percentage of trained shoppers (acting as patients) who received any written information

when receiving a new prescription and the quality of this information received from 306 randomly selected community pharmacies in 8 States. A panel of experts evaluated the written information for usefulness (as defined in the Keystone Action Plan) and quality, using explicit criteria. The results showed that of the 918 new prescriptions presented at pharmacies, the following occurred (Ref. 1):

- 87 percent were dispensed with CMI.
- 81 percent were dispensed with information that was considered unbiased in content and tone.
- 69 percent were dispensed with acceptable information about adverse drug reactions and what to do if an adverse drug reaction occurred.
- 68 percent were dispensed with acceptable information about the drug product and its indications for use.
- 49 percent were dispensed with acceptable directions about how to use the prescription drug product, receive maximum benefits from the drug product, and interpret the benefits of the drug product.
- 19 percent were dispensed with acceptable information about the drug products' contraindications and what to do if a contraindication existed.

FDA presented these 1999 study results at a public workshop held on February 29 and March 1, 2000 (Ref. 10).

A second study was performed in 2001 (the 2001 study) to determine whether the private sector had made further progress toward meeting the goal of Public Law 104–180. The 2001 study expanded upon the initial 1999 study and included 384 randomly selected pharmacies in 44 States. All CMIs received by trained shoppers (acting as patients) with new prescriptions at the pharmacy were sent to an expert panel (consistent with the 1999 study) to evaluate against eight general criteria described in the Keystone Action Plan. The criteria specified that the written patient information must include the following: (1) drug names and indications for use; (2) contraindications and what to do, if applicable; (3) specific directions about how to use, monitor, and get the most benefit; (4) specific precautions and how to avoid harm while using the prescription drug; (5) symptoms of serious or frequent adverse reactions and what to do; (6) general information, a disclaimer, and encouragement to ask questions; (7) scientifically accurate, unbiased, and up-to-date information; and (8) a written format that is legible and comprehensible to the consumer. Consumers were also recruited to

evaluate the written information and the extent to which the information was comprehensible, legible, and useful (Ref. 11).

The results of the 2001 study were presented in a final report to HHS and FDA in 2001 and were also published in 2005. The results showed that 89 percent of the 1,367 new prescriptions were dispensed with CMI (Refs. 11 and 12). However, the expert panel judged that fewer than 20 percent of CMI met the criteria for specificity, legibility, and comprehensibility (Ref. 11). Fewer than 10 percent of all leaflets met the quality criteria regarding contraindications, precautions, and how to avoid harm (Ref. 11). Assessments from consumers, consistent with assessments from expert panels, showed that most CMI did not meet the criteria (as described in the Keystone Action Plan) for font size, spacing, use of bullets, and reading difficulty. The 2001 study concluded that CMI “falls short of the information quality level required in the 1996 federal legislation,” and additional efforts were needed to meet the federally mandated distribution and quality goal (Ref. 11).

In the **Federal Register** of May 26, 2005 (70 FR 30467), we published a notice of availability of a draft guidance for industry entitled “Useful Written Consumer Medication Information (CMI).” In the **Federal Register** of July 18, 2006 (71 FR 40724), we published a notice of availability of a final guidance for industry (the 2006 CMI guidance, available at: <https://www.fda.gov/media/72574/download>). The 2006 CMI guidance is intended to assist organizations and individuals in developing useful CMI.

A third study, conducted in 2008 as a followup to the 1999 and 2001 studies, evaluated the quality and usability of CMI provided with new prescriptions. The results were presented to HHS and FDA in a final report published in 2008 (the 2008 study) (Ref. 13). This study used methods similar to those used in the 2001 study, but the 2008 study also incorporated information from the 2006 CMI guidance on developing useful written CMI. The 2006 CMI guidance, which was written in part based on the results of the 1999 and 2001 studies, assists individuals and organizations in developing useful written CMI.

The 2008 study included 365 pharmacies in 41 States (Ref. 13). The results indicated that although 94 percent of patients received CMI with new prescriptions, only about 70 percent of this information met the minimum criteria for usefulness, and a number of additional deficiencies were noted. Despite the FDA guidance, the

2008 study identified various shortcomings of the evaluated CMI, including lack of information about the management of the prescription drug product, significant redundancy of information that resulted in excessively long leaflets, poor formatting, and inadequate legibility and an inappropriately high reading level. Only half of CMI had specific information about what patients would need to monitor and manage when using their prescription drug therapies and actions to take when side effects or other problems occur. The 2008 study found that the length and format of CMI and the percent of items covered continued to vary considerably from pharmacy to pharmacy. The majority of CMI did not satisfy the criteria recommended in the 2006 CMI guidance. The 2008 study also noted that, although progress had been made, CMI continued to fall short of the Congressionally mandated goal of Public Law 104–180 that 95 percent of new prescriptions be accompanied by useful written patient information by 2006 (Ref. 13).

3. FDA 2007 Public Hearing

In the **Federal Register** of April 9, 2007 (72 FR 17559), we announced a public hearing entitled “Use of Medication Guides to Distribute Drug Risk Information to Patients” (the 2007 FDA public hearing) to be held on June 12 and 13, 2007 (Docket No. 2007N–0121). At the 2007 FDA public hearing, we obtained feedback and requested information and views on specific issues associated with the development, distribution, comprehensibility, and accessibility of Medication Guides. FDA officials heard testimony from one member of Congress; 40 individuals representing academia, consumers and consumer groups; the pharmaceutical industry; healthcare professional groups; physicians; pharmacists; and pharmacy organizations (Ref. 14). Although stakeholders stated it was important that patients receive appropriate risk information in the form of Medication Guides to make informed decisions about certain prescription drug products, stakeholders suggested that the current Medication Guide program was too cumbersome and lacked a standard distribution system. Stakeholders urged FDA to: (1) increase awareness of Medication Guides, (2) make Medication Guides easier to read and understand, (3) move toward facilitating the distribution of Medication Guides by electronic means, and (4) consider combining the information in Medication Guides with other information, such as CMI (Ref. 14).

4. Citizen Petition

In June 2008, we received a citizen petition (the 2008 citizen petition) from a large group of stakeholders representing pharmacy practice, medical consumers, and medical communications companies (Docket No. FDA–2008–P–0380). The 2008 citizen petition asked us to adopt an FDA-approved, concise, plain language, single-page patient information document for prescription drugs. The 2008 citizen petition requested that the one-page “single patient document” combine and simplify the many documents that patients currently receive at the pharmacy for prescription drug products (Ref. 15). In 2010, the petitioners voluntarily withdrew the 2008 citizen petition, citing FDA’s significant work and strides toward achieving the goals of the 2008 citizen petition with the ongoing development of PMI (Ref. 16).

5. The FDA Risk Communication Advisory Committee Meeting

In February 2009, the FDA Risk Communication Advisory Committee (RCAC), which included some members of the FDA Drug Safety and Risk Management Advisory Committee, met to explore approaches to improve the communication of prescription drug product information to patients, specifically regarding CMI, Medication Guides, and PPIs (Ref. 17). The RCAC recommended that FDA adopt a single standard document for communicating essential information about prescription drug products to patients. The single document was proposed as a replacement for CMI, Medication Guides, and PPIs. The RCAC also recommended that the standard document be FDA-approved and subject to a rigorous empirical evaluation of its effectiveness (Ref. 17).

We have determined that the current system fails to consistently provide patients with sufficient information to help them use prescription drug products safely and effectively. Based on the results of the 1999, 2001, and 2008 studies, comments from stakeholders at the 2007 FDA public hearing, the 2008 citizen petition, and recommendations from the 2009 RCAC, we are proposing a new type of Medication Guide to help patients use their prescription drug products safely and effectively.

6. Development of Prototypes

Prior to the development of this proposed rule, FDA developed prototypes for the proposed new type of Medication Guide, called PMI, based on

stakeholders’ input, research findings, and our knowledge and experience. To solicit further public input on the PMI prototypes and PMI in general, FDA held a public workshop, participated in a series of workshops convened by the Engelberg Center for Health Care Reform at the Brookings Institution (Brookings Institution), held a public hearing following the procedures set forth in part 15 (21 CFR part 15), and research was conducted on prototypes for PMI (OMB control number 0910–0691; Ref. 31).

C. History of the Rulemaking

1. FDA 2009 Public Workshop

On September 24 and 25, 2009, we convened a public workshop (the 2009 public workshop). Participants discussed the optimal content and format of written prescription drug product information to ensure that the information is comprehensible, accurate, and more easily accessible to patients (see 74 FR 33265, July 10, 2009, Docket No. FDA–2009–N–0295). The 2009 public workshop explored the following questions:

- What content is critical for patients to receive and in what order and format?
- How can access be improved?
- How should this information be distributed to patients?
- What parameters are appropriate with regard to evaluating the usefulness of the materials?

We prepared an issue paper to serve as context and background for the 2009 public workshop (Ref. 18).

At the 2009 public workshop, we presented four PMI prototypes for a fictitious drug that used different labeling formats. FDA developed the PMI prototypes based on stakeholders’ input, patient information studies and pilots, consumer-focused research, and our knowledge and experience with patient information and current labeling practices. All four PMI prototypes consisted of the same core content, including uses, side effects, what to do while taking the drug, what to avoid while taking the drug, and how to take the drug.

Prototype 1 was modeled on the format of the over-the-counter “Drug Facts” section of labeling (see 21 CFR 201.66), was one page in length, and was the most succinct (Ref. 19). Prototype 2 was modeled on the format of the “Highlights of Prescribing Information” section of labeling (see § 201.57(a) (21 CFR 201.57(a))), was one page, and was more detailed than Prototype 1 (Ref. 20). Prototype 3 was modeled on the format of the Prescribing Information (PI) and

contained two levels of information (see § 201.57). The first level summarized the information in a concise manner (similar to Highlights of Prescribing Information), and the second level explained the information in detail (similar to the Full Prescribing Information). Prototype 3 was two pages in length, appeared in question-and-answer format, and repeated information (Ref. 21). Prototype 4 was modeled on the current Medication Guide requirements (see part 208), was four pages in length, and was more detailed and comprehensive than the other three prototypes. It appeared in paragraph format and contained standard statements (Ref. 22).

During the 2009 public workshop, attendees identified the strengths and weaknesses of the four PMI prototypes pertaining to format, presentation, and context. Academic panelists described the key attributes and goals of written patient prescription drug product information as follows (Ref. 23):

- Patients should be able to understand what the prescription drug product is used for and how to use it appropriately.
- Patients should be able to find, understand, and retain information about the prescription drug product's contraindications and side effects.
- Patients should know where they can locate additional information about the prescription drug product that is not included in the written prescription drug product information.

Attendees also suggested that user testing of written prescription drug product information during the development stage should be mandatory to ensure that the final product is consumer friendly.

2. Brookings Institution Workshops and Distribution Studies

Based on a cooperative agreement with FDA, the Brookings Institution convened a series of four public workshops that discussed optimizing, implementing, and evaluating the adoption of PMI (Ref. 24).

On July 21, 2010, the Brookings Institution hosted the first workshop. Experts from academia, medical professional groups, stakeholders from the private sector (applicants, consumer organizations, and publishers of CMI), and FDA met to discuss improving written patient prescription drug product information. The following objectives were discussed at the workshop (Ref. 25):

- The overarching principles for effectively communicating prescription drug product information to patients.

- The metrics for evaluating CMI and the most useful content and format of a single paper document for prescription drug product information as represented in FDA's PMI prototypes.

- FDA's proposed strategy for evaluating the PMI prototypes.
- How patients will receive prescription drug product information in the future and whether this has implications for near-term initiatives centered around a single-document solution.

FDA further refined the PMI prototypes based on feedback provided at the first Brookings Institution workshop.

On October 12, 2010, the second Brookings Institution workshop was held to discuss strategies for making PMI easily accessible and how to most effectively distribute PMI to patients. As in July 2010, experts from academia and medical professional groups, stakeholders from the private sector (applicants, consumer organizations, and publishers of CMI), and representatives from FDA explored the following topics at the workshop (Ref. 26):

- Patient preferences for access to and distribution of PMI.
- Potential roles that applicants, publishers, distribution partners, pharmacists, and physicians can play in the development and distribution of PMI.
- Models for effective distribution of PMI within current and future healthcare delivery systems.
- Potential strategies for monitoring and ensuring the effectiveness of PMI.

The third Brookings Institution workshop was held on February 23, 2011. It summarized the first two Brookings Institution workshops and further discussed how to design pilot studies to test the distribution of PMI. The experts discussed the following topics (Ref. 27):

- The goals and objectives of demonstration pilots designed to evaluate feasibility of different methods to distribute the PMI prototype and to assess patient and provider preferences for the PMI prototype that was distributed to patients.
- How to develop a PMI prototype for use in the distribution pilots.
- The framework, development, and evaluation strategy for proposed distribution pilots.

As a result of discussions about PMI distribution at the third Brookings Institution workshop, Catalina Health (now Adheris Health) launched an 8-week quality improvement initiative in August 2012 to disseminate newly designed patient information to patients

filling prescriptions at participating pharmacies (Ref. 28). The newly designed patient information was based on FDA's PMI prototypes. Through voluntary telephone and online responses, Catalina Health: (1) surveyed patients to confirm that they received Catalina Health's patient information with their prescription drug product, (2) assessed whether they found the information useful, and (3) determined how they would like to receive this newly formatted patient information in the future. The results revealed that:

- More than 90 percent of patients recalled receiving Catalina Health's patient information and considered the written patient information useful (Ref. 28).
- The majority of patients surveyed (≥ 92 percent), across all age groups, reported that the new PMI was either "very useful" or "somewhat useful". Few respondents found this information to be either "not very useful" or "not useful at all" (≤ 9 percent across age groups). (Ref. 28).

On July 1, 2014, the Brookings Institution held a fourth public workshop to explore the following (Ref. 29):

- Lessons learned from health literacy researchers engaged in PMI projects.
- The role of stakeholders in moving the PMI initiative forward.

Stakeholders leveraged key findings from the previous three Brookings Institution workshops. Stakeholders developed methods and conducted research geared toward assessing the effectiveness of FDA's PMI prototypes and strategies to distribute PMI. Based on the previous findings and their research, the participants emphasized that enough information now exists to create effective PMI that will provide more value than currently available written prescription drug product information (Ref. 29).

3. FDA 2010 Part 15 Public Hearing

On September 27 and 28, 2010, we hosted a part 15 public hearing to solicit input on a new framework for the development and distribution of PMI to be provided to patients who are prescribed drug products. The purpose of the 2010 part 15 public hearing was to solicit input on the processes and procedures for standardizing PMI using a quality system approach for monitoring the development and distribution of PMI (see 75 FR 52765, August 27, 2010, Docket No. FDA-2010-N-0437).

The hearing was attended by experts from academia, medical professional groups, stakeholders from the private sector (applicants, consumer

organizations, and publishers of CMI), and FDA. Presentations and comments from the attendees offered support for the following principles:

- PMI should be available at pharmacies and should use the existing distribution capabilities of the pharmacy.
- FDA should have an active role in the development and approval of PMI and should design content and format guidelines.
- Plain language should be used to increase comprehension.
- PMI should be consumer tested.
- A range of distribution methods should be used for PMI.

However, attendees disagreed on whether the length of PMI should be limited to one page (Ref. 30).

4. FDA's Research on PMI Prototypes

In developing the four PMI prototypes, FDA focused on creating a standardized format that patients would become familiar with to help them use and understand PMI. Based on the RCAC recommendations, discussions from the 2009 public workshop, the Brookings Institution workshops, the 2010 part 15 public hearing, and comments from stakeholders, we further narrowed down our four PMI prototypes to two PMI prototypes. The two PMI prototypes tested, formatted in either "Bubbles" or "Over-the-Counter" formats, were based on existing Medication Guide regulations, and developed to be representative of real Medication Guides. These prototypes were selected through an iterative process involving recommendations and empirical data gleaned from several sources, including: (1) input from the previously mentioned entities (*e.g.*, public stakeholders and risk communication experts from government, industry, and academia (Ref. 17)); (2) the application of plain language principles to the content and formatting of these handouts; and (3) findings from qualitative research with patients who had one of the medical conditions (*e.g.*, rheumatoid arthritis) that the fictitious drug described in these PMI prototypes (*i.e.*, Rheutopia) was indicated to treat (Ref. 17).

We announced our research study entitled "Experimental Study of Patient Information Prototypes" and requested comments on the proposed collection of information (75 FR 23775, May 4, 2010, Docket No. FDA-2010-N-0184). We explained that the study was designed to use different prototypes to test whether consumers were able to comprehend serious warnings, directions for use, drug indications and

uses, contraindications, and side effects in the material presented.

In the 2012, RTI International, contracted by FDA, conducted a research study using variations of the two PMI prototypes to test different ways of presenting information about prescription drug products to patients who had obtained a prescription drug product. The study examined the impact of the PMI prototypes on outcomes, including perceived risk, recall, and ease of understanding the information.

The research study included qualitative components and quantitative components to assess the comprehension and the use of the two PMI prototypes for a fictitious drug, Rheutopia, in individuals with and without the chronic health condition for which Rheutopia was indicated. The qualitative phase of RTI International's research explored preferences for format and font used in the PMI prototypes and assessed readability and comprehension. The quantitative phase of RTI International's research investigated whether either of the two PMI prototypes resulted in better recall of the information, increased perceived risk, or increased ease of understanding. The results suggest that content and format may be important predictors of recall of factual information about prescription drug products. We used the results of the 2012 research study in conjunction with additional research to develop several aspects of this proposed rule (Ref. 31).

The information obtained from the hearings, the results of the research performed, and the recommendations provided by stakeholders highlights the importance of providing clear, concise, and accessible information to patients as this may help them to use their prescription drug products safely and effectively.

IV. Legal Authority

In this proposed rule, FDA is addressing legal issues relating to FDA's proposed action to revise the regulations regarding format and content for prescription drug labeling. Our proposed revisions to the format and content requirements for prescription drug labeling are authorized by the FD&C Act (21 U.S.C. 321 *et seq.*) and by the PHS Act (42 U.S.C. 262 and 264).

The FD&C Act provides that a drug shall be deemed to be misbranded if the requirements of section 502 of the FD&C Act are not met (21 U.S.C. 352). This provision applies to all drugs, including those that are also regulated as biological products under the PHS Act. In addition, section 351(b) of the PHS

Act (42 U.S.C. 262(b)) provides that "no person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark."

Section 502(f) of the FD&C Act deems a drug to be misbranded if its labeling lacks adequate directions for use and adequate warnings against use in those pathological conditions where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users. This section of the FD&C Act further authorizes FDA, on authority delegated from the Secretary, to issue regulations exempting a drug or device from the requirement to bear adequate directions for use upon a determination that such directions are not necessary for the protection of users.

It is well-established that a drug must have adequate directions for use unless the drug is exempt from that requirement by regulation. For a prescription drug to avoid being misbranded under section 502(f) of the FD&C Act, its labeling must conform to regulations issued by FDA. (See, *e.g.*, *U.S. v. Articles of Drug*, 625 F.2d 665, 672 (5th Cir. 1980).) FDA has, since 1952, had a regulation that states the conditions under which a prescription drug must be labeled in order to be exempt from the adequate directions for use requirement. (See 17 FR 6818 (July 25, 1952).) The current version of that rule is codified in § 201.100 (21 CFR 201.100). This proposed rule, if finalized, would modify the existing exemption from adequate directions for use for prescription drugs (§ 201.100). We are proposing this rule based on our determination that an additional condition must be present for a prescription drug to be exempt from the requirement to provide adequate directions for use. This additional condition is that, when PMI is required under part 208 or proposed § 606.123 (21 CFR 606.123), the drug must have FDA-approved PMI and be dispensed with such PMI (as described in proposed part 208 or § 606.123) as applicable.

In addition, section 502(a) of the FD&C Act deems a drug to be misbranded "if its labeling is false or misleading in any particular." Under section 201(n) of the FD&C Act (21 U.S.C. 321(n)), when considering whether labeling is misleading, FDA shall consider whether the labeling fails to reveal facts that are material with

respect to consequences that may result from the use of the drug under the conditions of use prescribed in the labeling or advertising thereof or under usual or customary conditions of use. If a prescription drug does not have PMI after it is required for that drug, its labeling will fail to reveal material information to patients.

Furthermore, the premarket approval provisions for drugs require that product labeling adequately address the safety and effectiveness of the drug product. Under section 505 of the FD&C Act (21 U.S.C. 355), we will approve an NDA only if the drug is shown to be both safe and effective for use under the conditions set forth in the drug's labeling. Under 21 CFR 314.125, we will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of 21 CFR part 201. Under section 351(a)(2)(C)(i)(I) of the PHS Act, we are authorized to license a biological product only upon a demonstration that the biological product is safe, pure, and potent. This demonstration would be assessed in the context of the labeling for that product.

Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes us to issue regulations for the efficient enforcement of the FD&C Act. Section 361 of the PHS Act (42 U.S.C. 264) authorizes us to make and enforce regulations determined to be necessary to prevent the introduction, transmission, or spread of communicable disease into the United States or from one State or possession into any other State or possession. For blood and blood components intended for transfusion on an outpatient basis, the proposed requirement to include information on the risks associated with blood transfusion, including transfusion-transmitted infections, in PMI may aid in preventing the introduction, transmission, or spread of communicable disease.

Furthermore, section 505–1 of the FD&C Act, authorizes FDA to require a Medication Guide, such as PMI, as one element of a REMS when necessary to help mitigate a serious risk of the prescription drug product.

With regard to generic drug products, section 505(j)(2)(A)(v) of the FD&C Act requires an ANDA to include information showing that the proposed generic drug product's labeling is the same (with some exceptions) as the labeling approved for the corresponding RLD. Thus, because under this proposal PMI will be approved drug labeling, FDA has authority to require drug

product manufacturers seeking approval of ANDAs to adopt PMI that is the same as the PMI for the RLD, if an approved PMI for their RLD exists, except that the PMI for the ANDA could reflect certain permissible differences in accordance with section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)). If the ANDA is already approved when the PMI for its RLD is first approved, FDA believes it is appropriate that the ANDA product also adopt PMI that is the same as that approved for the RLD, except that again, the PMI for the ANDA could reflect certain permissible differences. The statutory bases for this requirement with respect to approved ANDAs are the misbranding provisions cited previously. Where an ANDA applicant seeks approval of an ANDA referencing a listed drug whose approval has been withdrawn and for which no PMI was approved for the RLD before the approval of the RLD was withdrawn, the ANDA applicant must submit PMI that corresponds to an FDA-created template once FDA has provided a template. Again, the statutory bases for this requirement are the misbranding provisions.

We note that Federal courts have affirmed that FDA has authority to require the dispensing of patient labeling for prescription drugs and that such requirements do not interfere with the practice of medicine. (See *Pharmaceutical Manufacturers Association v. Food and Drug Administration*, 484 F. Supp. 1179 (D. Del. 1980), *aff'd per curiam*, 634 F. 2d 106 (3rd Cir. 1980).)

V. Description of the Proposed Rule

We are proposing to revise the part heading and all subparts of current part 208. The part heading would be revised to “Medication Guides.” FDA is proposing to require a new type of Medication Guide for patients that will be called PMI. These proposed requirements for patient labeling would ensure that clear, concise, accessible, and useful written prescription drug product information would be delivered to patients in a consistent and easily understood format to help patients use all of their prescription drug products safely and effectively when dispensed in an outpatient setting.

Proposed part 208 (Medication Guides) would be the successor regulation to current part 208 (Medication Guides for Prescription Drug Products). Therefore, current Medication Guides would continue to be available as a potential element of a REMS under section 505–1(e) of the FD&C Act as described in section V.J of

this document until FDA has approved PMI for the prescription drug product.

Consistent with proposed part 208, FDA is proposing to add § 606.123 to part 606, subpart G, to require establishments that collect blood and blood components intended for transfusion to create and distribute PMI consistent with proposed part 208.

A detailed description of the proposed revisions and a description of each proposed section are provided in sections V.A through V.L of this document.

A. Placement and Removal of the Current Requirements for Medication Guides for Prescription Drug Products (Proposed §§ 208.91, 208.92, 208.94, 208.96, and 208.98)

Medication Guides are currently required under part 208 for certain prescription drug products that FDA determines pose a serious and significant public health concern, requiring distribution of FDA-approved patient information. Medication Guides contain information that FDA believes is necessary to a patient's safe and effective use of a prescription drug product. Once a prescription drug product has FDA-approved PMI, its current Medication Guide requirement (if any) would no longer be applicable (see also discussion in section V.J of this document). FDA would withdraw the current regulations governing Medication Guides in part 208 after all prescription drug products that had Medication Guides have FDA-approved PMI.

We believe it is important that patients continue receiving FDA-approved patient information for prescription drug products that we previously determined posed a serious and significant public health concern during the implementation of the final rule. Therefore, we propose that the provisions in current part 208 requiring Medication Guides for select prescription drug products would remain in effect as described in section V.J of this document.

For current part 208 to remain in effect until all prescription drug products that had Medication Guides have FDA-approved PMI, we propose that current §§ 208.1 and 208.3 be relocated to §§ 208.91 and 208.92, subpart C, respectively. Current §§ 208.20, 208.24, and 208.26 would be relocated to proposed §§ 208.94, 208.96, and 208.98, subpart D, respectively. The definitions in proposed § 208.92 would be revised for clarity and consistency with definitions in proposed § 208.20; however, the substantive meaning of the definitions would remain the same.

B. Removal of the Requirements for Patient Package Inserts (Proposed §§ 310.501 and 310.515)

PPIs for oral contraceptives and estrogen-containing drug products are required under §§ 310.501 and 310.515, respectively. PPIs provide detailed information to patients about the benefits and risks involved with using these prescription drug products and contain information to help patients use them safely and effectively. We have determined that once an oral contraceptive or estrogen-containing prescription drug product has FDA-approved PMI, PPIs would no longer be necessary for the safe and effective use of these products (see also discussion in section V.J of this document). FDA would withdraw the current regulations in §§ 310.501 and 310.515 for NDAs, BLAs, and ANDAs that have FDA-approved PPIs after all such prescription drug products have FDA-approved PMI.

We believe it is important that patients continue to receive FDA-approved patient information for oral contraceptives and estrogen-containing products during the implementation of PMI. Therefore, we propose that §§ 310.501 and 310.515 would remain in effect as described in section V.J of this document.

Under this proposed rule, when finalized, we would no longer accept voluntary submissions of PPI for prescription drug products. Prescription drug products used, dispensed, or administered on an outpatient basis would be required to have FDA-approved PMI, with the exception of excluded products identified in proposed § 208.10(d).

C. Scope and Purpose (Proposed §§ 208.10 and 606.123)

Currently, Medication Guides are required only for prescription drug products that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. In contrast, when finalized, this proposed rule would require the creation and distribution of a new type of Medication Guide, called PMI, for any prescription drug product that is approved or submitted for approval under section 505 of the FD&C Act that is used, dispensed, or administered on an outpatient basis with the exception of excluded entities identified in proposed § 208.10(d). For the purposes of this proposed rule, a drug product also includes a biological product licensed under section 351(a) or (k) of the PHS Act. PMI would improve public health

by providing patients with clear, concise, accessible, and useful written prescription drug product information delivered in a consistent and easily understood format to help patients use their prescription drug products safely and effectively.

PMI content would be based on information required in the PI as described in §§ 201.56, 201.57, and 201.80 (21 CFR 201.56, 201.57, and 201.80), and/or the circular of information described in § 606.122 (21 CFR 606.122). In cases where marketing of an application has been discontinued but approval of the application has not been withdrawn under 21 CFR 314.150 or section 505(e) of the FD&C Act, the applicant must continue to comply with all applicable statutory and regulatory requirements, including the requirements set forth in this proposed rule, if finalized.

Authorized dispensers would be required to provide patients with FDA-approved PMI, when such PMI exists, each time a prescription drug product is used, dispensed, or administered on an outpatient basis. This would ensure that patients receive the information to help them use their prescription drug products safely and effectively. Prescription drug products used, dispensed, or administered on an outpatient basis are those prescription drug products that are dispensed outside of an inpatient setting (which include a hospital or long-term care facility, such as a nursing home or rehabilitation facility). The most common outpatient settings are retail pharmacies and hospital ambulatory care pharmacies, where the patient takes the prescription drug product home and uses it. Outpatient settings also include those in which the prescription drug product is dispensed to a healthcare provider who administers it to the patient. This includes, but is not limited to, clinics, healthcare providers' offices, dialysis centers, and infusion centers, including those administering blood and blood component transfusions. In all of these outpatient settings, we believe that patients should be able to take home important information about the prescription drug product, such as information about potential side effects that may occur, when to notify a healthcare provider, or followup that may be required after receiving a prescription drug product.

PMI would not be required for prescription drug products used, dispensed, or administered by a healthcare provider in an emergency (for example, an emergency room visit), including a public health emergency setting, including natural and/or

human-made disasters, or an inpatient setting (for example, a hospital or a nursing home). PMI would not be required for a product under Emergency Use Authorization, which may require patient or provider Fact Sheets. In these situations, a healthcare provider provides the patient or a patient's caregiver with information about the drug product and the potential side effects that may occur and also answers questions the patient may have. Further, in these situations and settings, the healthcare provider is responsible for monitoring the patient, as necessary, after the prescription drug product is used, dispensed, or administered. Finally, Emergency Use Authorizations are not FDA approved applications; therefore, products authorized under Emergency Use Authorizations would not require PMI.

With few anticipated exceptions, we propose to exclude manufacturers of preventive vaccines that do not have a Medication Guide from the requirement to create and distribute PMI. The Centers for Disease Control and Prevention (CDC) manages a comprehensive preventive vaccine program that includes providing information on preventive vaccines to patients. We have determined that the current system for developing and providing vaccine information statements (VISs) to patients meets the goal of PMI for these products. Under the National Childhood Vaccine Injury Act of 1986, the Secretary is required to develop and disseminate vaccine information materials for distribution by all U.S. healthcare providers (see section 300aa-26 of the National Childhood Vaccine Injury Act of 1986 (42 U.S.C. 300aa-1 to 300aa-34)). Healthcare providers must distribute the information to patients (or the parent or legal representative of a child) who receive vaccines under the National Vaccine Injury Compensation Program of 1986 (NVICP) (Pub. L. 99-660). Development and revision of VISs have been delegated to CDC. CDC also develops VISs for vaccines that are not covered by NVICP. VISs are available on the internet at <https://www.cdc.gov/vaccines/hcp/vis/current-vis.html>.

D. Definitions (Proposed § 208.20)

This proposed rule would provide definitions for the purposes of this rule for the terms *administered*, *applicant*, *authorized dispenser*, *dispensed*, *drug name*, *drug product*, *licensed healthcare provider*, *manufacturer*, *patient*, *Patient Medication Information*, *revision date*, and *used*. This proposed rule would also revise definitions from current part 208 for clarity and consistency;

however, the substantive meaning of those definitions would remain the same.

Specifically, this proposed rule would define *authorized dispenser* as an individual(s) or entity who is licensed, registered, or otherwise permitted by the jurisdiction in which the individual(s) or entity practices to provide prescription drug products in the course of professional practice. We believe that, in most instances, the authorized dispenser will be a pharmacist. However, an authorized dispenser may also include physicians, nurses, or other licensed healthcare providers legally permitted under State law to provide prescription drug products to patients.

This proposed rule would also define *Patient Medication Information* as a type of Medication Guide—a form of patient labeling—which meets the requirements set forth in this proposed rule. PMI would be labeling under section 201(m) of the FD&C Act.

E. Requirements for the Format of Patient Medication Information (Proposed § 208.30)

The proposed rule would establish the general format requirements for PMI (see proposed § 208.30). The proposed rule would require PMI to have a uniform format that will make it easier for patients to read, understand, and use PMI. The formatting of written patient prescription drug product information has a large effect on the ease of understanding and use of the information (Ref. 32). The formatting requirements are consistent with the guidelines from patient education experts (Refs. 32 and 33). These formatting requirements are intended to make it easier for patients to read and comprehend the important information contained in PMI and help them use their prescription drug products safely and effectively (Refs. 32 and 33).

Consistent with current FDA regulations (see § 201.15(c)(1) (21 CFR 201.15(c)(1))), the proposed rule would require that PMI be written in the English language; provided, however, that in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English (see proposed § 208.30(a)(1)).

FDA strongly encourages applicants to work with retailers and other organizations to ensure that PMI is accessible to individuals with limited English proficiency. To the extent an applicant, retailer, or other organization receives Federal financial assistance from HHS, they are required to take

reasonable steps to provide meaningful access to their programs and activities by individuals with limited English proficiency under Title VI of the Civil Rights Act of 1964 and its implementing regulations.²

Currently, translations in languages other than English of written prescription drug information (including Medication Guides and Patient Package Inserts) are provided in numerous ways—by drug applicants, retailers, and other organizations. These organizations create written translations of medication information, and they also provide live oral sight translations by an interpreter (for example, via telephone) of medication information in multiple languages. For example, the American Society of Health-System Pharmacists provides more than 1,500 monographs covering prescription and nonprescription drugs in both English and Spanish.³ Translations of PMI could similarly be made available by retailers and other organizations.

In accordance with current FDA regulations at § 201.15(c)(1) and proposed § 208.30(a)(1), when PMI is provided in a language other than English it must be distributed along with English language PMI, with the limited exception of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English (and PMI is provided in such predominant language).

FDA acknowledges the benefits of having translated prescription drug information for individuals with limited English proficiency. This proposed rule provides flexibility to allow for multiple approaches to provide access to PMI for individuals with limited English proficiency through a variety of different mechanisms. FDA seeks further information regarding what actions applicants and other organizations might take to make PMI accessible to individuals with limited English proficiency.

The proposed rule would require that PMI be provided to a patient in paper format and be legible and printed on a single side of an 8½ by 11-inch sheet of paper and not exceed one page (see proposed § 208.30(a)(2)). Studies show that patients prefer a simplified one-page format for written patient information and are more likely to read

information that is short and concise (Refs. 34 and 35). Studies also show that patients understand more information when it is contained in a shorter document and are better able to understand information when it is presented in a simplified one-page format (Refs. 34, 36, and 37). In contrast, patients are often overwhelmed by and have difficulty understanding lengthy patient information materials (Refs. 35 and 38).

We have determined that written patient prescription drug product information can be appropriately provided in a single page. For example, FDA has successfully created one-page Medication Guides for extended-release and long-acting opioid analgesics (Ref. 39) and immediate-release opioid analgesics. As stated previously, this one-page format is also supported by feedback obtained from stakeholder input, advisory committees, workshops, and public hearings.

As discussed in section V.K of this document, proposed § 208.90 would allow for a waiver from one or more of the proposed requirements for PMI if we determine that any requirement is inapplicable, unnecessary, impracticable, or contrary to patients' best interests for a particular prescription drug product. We envision rarely granting a waiver to the one-page format requirement. FDA may consider an applicant's request for an extension from the specified implementation date to fully comply with the PMI requirements. Such requests will be evaluated on a case-by-case basis. Under this proposed rule, PMI would be stored electronically in a central repository managed by FDA (as discussed in section VI of this document). The proposed rule would require that PMI provided in electronic format be printable to ensure that all patients have access to the written patient prescription drug product information, including patients who do not have access to the electronic version of PMI (see proposed § 208.30(a)(3)). To maintain standardization for ease of use by patients, electronic and printed PMI must be identical and meet the format and content requirements specified in this proposed rule.

The proposed rule would require that all headings and subheadings (as required in proposed § 208.40(b) and (c)(2)) and that the title "PATIENT MEDICATION INFORMATION" (as required in proposed § 208.40(a)(5)) appear in bold type (see proposed § 208.30(a)(4)). The proposed rule would also require bold type for the drug name(s), phonetic spelling of the drug name(s), dosage form(s), and

² 42 U.S.C. 2000d, *et seq.*; 45 CFR part 80; *see also* Section 1557 of the Affordable Care Act, 42 U.S.C. 18116, which provides similar protections as those under Title VI in health programs and activities receiving Federal financial assistance.

³ <https://www.ashp.org/products-and-services/database-licensing-and-integration/ashp-patient-medication-information>.

route(s) of administration listed at the top of the page on the line immediately below the title "PATIENT MEDICATION INFORMATION" (see proposed § 208.30(a)(4)). Bold headings would introduce each section and draw distinction between sections. We believe that the use of bold type would emphasize PMI headings and help patients scan for information contained in PMI (Ref. 40). Only PMI headings, subheadings, the title "PATIENT MEDICATION INFORMATION," and the drug name(s), phonetic spelling of the drug name(s), dosage form(s), and route(s) of administration at the top of the page must appear in bold type. The drug name(s) used in other parts of PMI must not appear in bold. In general, bold text should not be used for any other information in the document.

The proposed rule would require the title "PATIENT MEDICATION INFORMATION" to appear in all uppercase letters. Using all uppercase letters for the title will alert patients to the purpose of the document. The proprietary name (if any) of the prescription drug product may be presented in all uppercase letters. Generally, no other words may be presented in all uppercase letters with the exception of commonly used acronyms (for example, GERD in place of gastroesophageal reflux disease) (see proposed § 208.30(a)(5)). However, when an acronym is used, it should be defined the first time it appears in PMI (for example, gastroesophageal reflux disease (GERD)). Other information should be composed of both uppercase and lowercase type or just lowercase type. The use of text set in all uppercase type is more difficult to read (Ref. 41). The proprietary name of the prescription drug product, if used, may be written in all uppercase type, which will prominently display the proprietary name so patients can easily identify and associate PMI with the correct prescription drug product. For drug products without a proprietary name, the nonproprietary name should be written in title case letters.

The proposed rule would require that the title "PATIENT MEDICATION INFORMATION" (as described above) and the drug name(s), phonetic spelling of the drug name(s), dosage form(s), and route(s) of administration beginning immediately below the title must appear centered at the top of the page (see proposed § 208.30(a)(6)). This will ensure that the title and purpose of the document are easy for patients to find.

The proposed rule would require that PMI be presented in a minimum of 10-point font with 1 point equal to 0.0138 inches (see proposed § 208.30(b)(1)).

This size type is intended to make it easier for patients to read the important information contained in PMI (Ref. 33). This proposed requirement applies to all sections of PMI except the name and address of the manufacturer, packer, and/or distributor; the U.S. license number of the prescription drug product that is a biological product; the statement "The content of this Patient Medication Information has been approved by the U.S. Food and Drug Administration;" and the revision date.

The proposed rule would prohibit PMI from containing any reverse type (such as white or neutral color type on a darker color background), lightface, shading, condensed type, or narrow fonts (see proposed § 208.30(b)(2)). These effects can make reading more difficult for patients (Ref. 40).

The proposed rule would prohibit PMI from containing any colors other than black type to facilitate readability for patients (see proposed § 208.30(b)(3)). Black type on a white background maximizes contrast and therefore legibility of words (Ref. 40). Furthermore, certain colors and combinations of colors do not print clearly on paper (Ref. 41). This proposed requirement also considers feedback from stakeholders regarding pharmacies' printing limitations (for example, certain pharmacies are limited to printing in black and white).

Because PMI is a one-page document, the proposed rule would prohibit PMI from containing a page number (see proposed § 208.30(b)(4)). This would prevent patient confusion if the applicant submits PMI to FDA with other documents that may include page numbers.

We are proposing that pictograms and icons not be used in PMI for several reasons. For example, research indicates that different cultures may have different interpretation of pictograms and icons (Refs. 40 and 42). Pharmacies' printing limitations were also taken into consideration.

F. Requirements for the Content of Patient Medication Information (Proposed § 208.40)

We propose that PMI would highlight the most important information that patients need to know to help them use their prescription drug products safely and effectively. PMI is not intended to be a substitute for the PI described in §§ 201.56(d), 201.57, and 201.80 or the circular of information described in § 606.122 (while PMI would highlight the most important information, it is not intended to and would not include all the essential scientific information needed for the safe and effective use of

the drug) or to be a replacement for patient counseling by a healthcare provider. PMI, while meant to help patients safely and effectively use prescription drug products, would not be considered to be adequate directions for use as described in 21 CFR 201.5. Rather, PMI would be provided to patients with prescription drug products that are used, dispensed, or administered on an outpatient basis to help them safely and effectively use the prescription drug product.

In determining specific headings and information to be included in PMI, we researched scientific literature, conducted studies examining several PMI prototypes, held public workshops and hearings, and obtained stakeholder input on what information patients need in order to use their prescription drug products safely and effectively. The proposed content of PMI would highlight essential information found in the PI that the patient needs to know about the prescription drug product and would include basic directions on how to use the prescription drug product. Some information included in the drug product's PI may not be regularly included in PMI. Detailed instructions for use that cannot be adequately conveyed in PMI would continue to be approved by FDA in other labeling (for example, in the PI or in the Instructions for Use for the drug product).

The proposed rule would require PMI to be written in terms that are likely to be read and understood by most individuals (see proposed § 208.40(a)(1)). The use of overly technical language may deter patients from reading and understanding the important information contained in PMI. Based on the National Adult Literacy Survey, nearly half of the U.S. adult population is functioning at or below an eighth-grade reading level (Ref. 43). Other studies have also found that the average American adult reads at an eighth-grade or ninth-grade reading level (Ref. 44). The Keystone Action Plan advocates that prescription drug product information intended for patients be written at a sixth-grade through eighth-grade reading level (Ref. 9).

We believe that the approaches taken will help to improve accessibility of medication information for all patients, including patients with low health literacy, who may be dispensed a prescription drug product in an outpatient setting. FDA seeks comment on whether the proposed format and content requirements support the accessibility of patient medication information for all intended users,

including patients with low health literacy.

FDA is aware that consumer testing, such as the testing of readability and comprehension, may be used to inform the development of written patient materials such as PMI and may improve the usability of these materials. We are not proposing to require consumer testing for PMI at this time, because FDA lacks empirical evidence demonstrating that consumer-tested PMI directly results in benefits to patients over non-consumer-tested PMI. However, FDA recognizes the potential value in consumer testing and is aware that some stakeholders are engaged in consumer testing of written patient materials for their drug products. We note that FDA carefully considered the question of whether consumer testing of PMI would be an appropriate requirement for this regulation, and we understand that some stakeholders advocate for the requirement of such testing to increase the potential usefulness of the PMI. In response to this proposal, we invite comment on this question, and in particular, the submission of empirical evidence supporting the value of such consumer testing. We also ask those in the public who would oppose a requirement of consumer testing to submit comments explaining their position on this issue. FDA will consider this option as a requirement in the final rule if compelling evidence concerning the value of consumer testing is submitted.

Rather than require consumer testing, FDA is considering the establishment of a publicly available database, potentially through a public-private partnership, of consumer-tested phrases and terms that would assist in the development of written patient materials, including PMI. FDA expects to implement the use of common terms and consistent descriptions as part of the patient labeling review process, when appropriate, across drug products to facilitate consumers' understanding of these phrases and terms across written materials, including PMI. FDA seeks comments on the development and maintenance of such a database.

The proposed rule would require that PMI must not be promotional in tone (see proposed § 208.40(a)(2)). As noted above, the primary purpose of PMI is to highlight the most important information that patients need to know to help them use their prescription drug products safely and effectively. This approach of conveying important information in an objective manner is consistent with the existing regulatory provision pertaining to the FDA-approved PI that states that a

prescription drug product's PI must not be promotional in tone (§ 201.56(a)(2)). This proposed rule is not intended to address the use of other avenues, outside of PMI, to communicate to patients, including to provide promotional messaging.

The proposed rule would also require PMI to be scientifically accurate, not to be false or misleading in any particular, and to be based on and consistent with the prescription drug product's PI, as described in §§ 201.56, 201.57, and/or 201.80 or in the circular of information described in § 606.122 (see §§ 202.1 and 201.100(d)(1) and section 505 of the FD&C Act (see proposed § 208.40(a)(3)). The proposed rule would require that PMI for NDAs and BLAs be updated when new information becomes available that would cause PMI to become inaccurate, false, or misleading in accordance with § 314.70 (21 CFR 314.70) and § 601.12 (21 CFR 601.12) (see proposed § 208.40(a)(3)). This provision would require that PMI for ANDAs be updated when the PMI for the RLD is updated or the FDA-created template is updated (for ANDAs with withdrawn RLDs).

The proposed rule would require that the title "PATIENT MEDICATION INFORMATION" appear at the top of the page (see proposed § 208.40(a)(4)). This title would inform readers that the document has prescription drug product information intended for patients.

The proposed rule would require that the drug name(s) be listed at the top of the page on the line below the title, "PATIENT MEDICATION INFORMATION" (see proposed § 208.40(a)(5)). We propose that the phonetic spelling(s) of the proprietary name (if any) and the established name (or the proper name) must also be included to help the patient pronounce the name(s) of the prescription drug product. If the drug name is used again throughout the PMI, only the proprietary name (if any) would be used. Those prescription drug products not having a proprietary name would use the established name or the proper name.

The proposed rule would require the statement "The content of this Patient Medication Information has been approved by the U.S. Food and Drug Administration" to appear at the bottom of the page, followed by the revision date (see proposed § 208.40(a)(6)). The revision date would be the initial date the first PMI was approved or the date on which any changes have been made to PMI, whichever applies and is later, and would appear in numeric format (for example, Revised: 10/2025). This would alert patients to any revision to

the PMI since the patient last received the information.

The proposed rule would require that the name and place of business of the manufacturer, packer, or distributor of the prescription drug product that is not a biological product appear in the PMI below the statement required in § 208.40(a)(6) and the revision date (see proposed § 208.40(a)(7)). The proposed rule would require the licensed manufacturer's name, address, and U.S. license number of the prescription drug product that is a biological product to appear in the PMI (the distributor's or marketer's name and address may also be included) (see proposed § 208.40(a)(7)). The authorized dispenser may include their name and place of business. While the manufacturer or distributor information may be available on the original carton or container for the product or in the prescribing information, patients generally do not receive the carton or container or the prescribing information when the prescription drug product is dispensed at a pharmacy. Thus, including this information on the PMI helps to ensure the patient receives it.

The proposed rule would require that any heading, subheading, or specific information (see proposed § 208.40(b) and (c)) that is clearly inapplicable to the prescription drug product be omitted from the PMI (see proposed § 208.40(a)(8)) because such heading or specific information is not required for the patient to safely or effectively use the prescription drug product. The omission of any required heading, subheading, or specific information would be indicated only in the absence of the required heading, subheading, or specific information in the PMI.

The proposed rule would require specific headings in the following order: "[Insert drug name] is," "Important Safety Information," "Common Side Effects," and "Directions for Use" (see proposed § 208.40(b)). The use of headings helps to highlight specific information and helps patients locate information in the document and better understand it (Refs. 45 and 46). The proposed rule would require the headings to appear in a specified order and would ensure consistency in formatting for all PMI. This proposed requirement would help patients become familiar with both the type and location of relevant information in PMI. This will help them to quickly and accurately locate information about how to safely and effectively use the prescription drug product (Ref. 47).

The proposed rule would require specific information to be included under each required heading (see

proposed § 208.40(c)). We propose that the information in each section must be concise and based on and consistent with the prescription drug product's PI.

Under the heading, “[Insert Drug Name] is,” the proposed rule would require a concise summary of the approved outpatient indications and uses of the prescription drug product listed in the prescription drug product's PI (see proposed § 208.40(c)(1)). The information in this section would be consistent with the information found in the INDICATIONS AND USAGE section of the PI. FDA is aware that certain prescription drug products have a large number of approved indications and uses. Therefore, this section of PMI is not meant to list all approved indications and uses verbatim as described in the PI, but rather to summarize the approved outpatient indications and uses in language that is most useful for patients.

Under the heading “Important Safety Information,” the proposed rule would require specific subheadings in the following order: “Warnings,” “Do not take,” “Serious side effects,” and “Tell your health care provider before taking” (proposed § 208.40(c)(2)).

The proposed rule would require the subheading “Warnings” to be followed by a concise summary of serious warnings, including those that may lead to death or serious injury from the use of the prescription drug product (see proposed § 208.40(c)(2)(i)). The “Warnings” subheading must include a summary of the information found in the prescription drug product's boxed warning, if any, that is most relevant for patients to know for the safe and effective use of the prescription drug product.

The proposed rule would require the subheading “Do not take” to be followed by a statement of the circumstances (if any) in which the prescription drug product should not be used because the risk of use outweighs any benefit (see proposed § 208.40(c)(2)(ii)). The information in the “Do not take” subheading would be consistent with the most relevant information to patients found in the “CONTRAINDICATIONS” section of the PI. Because PMI is intended to aid patients on how to safely and effectively use their prescription drug product after it has been prescribed, patients need to be aware of contraindications (if any) associated with the prescription drug product.

The proposed rule would require the subheading “Serious side effects” followed by: (1) a listing of the clinically significant adverse reactions or risks associated with the use of the

prescription drug product that are most relevant to the patient and (2) information on when to call a healthcare provider or when and how to obtain emergency help if certain clinically significant adverse reactions occur (see proposed § 208.40(c)(2)(iii)). The information under this subheading must be consistent with either: (1) the most relevant information to patients found in the “WARNINGS AND PRECAUTIONS” section for drug labeling that must meet the format and content requirements of §§ 201.56(d) and 201.57 or (2) the “WARNINGS” section and the “PRECAUTIONS” section for drug labeling that must meet the format and content requirements of § 201.80. Side effects that may not meet the preceding criteria may still be considered serious side effects when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed (see FDA Guidance for Industry, “Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format,” January 2006 (available at <https://www.fda.gov/media/72139/download>)).

The proposed rule would require the subheading “Tell your health care provider before taking” followed by a statement that identifies specific populations and conditions that may have clinically important differences in response to the prescription drug product or may change the recommendation for use of the prescription drug product (for example, pregnancy or lactation) (see proposed § 208.40(c)(2)(iv)).

Under the heading “Common Side Effects,” the proposed rule would require a statement of frequently occurring adverse reactions from the use of the prescription drug product (see proposed § 208.40(c)(3)). The listed common side effects would have to be consistent with the “ADVERSE REACTIONS section” of the prescription drug product's PI. Under this heading, the most common adverse reactions that would be listed are those that are likely to be caused by use of the drug product or that are meaningful to the patient in terms of seriousness and frequency. We propose that the listed common side effects must focus on the most clinically relevant and the important adverse reactions to inform the patient. In determining whether a less common adverse reaction should be included, consideration may be given to a combination of factors, which include the seriousness of an adverse reaction, the likelihood that the reaction could

affect patients' adherence or continuation of therapy, and the importance of identifying the adverse reaction and treating it at an early stage (see FDA Guidance for Industry, “Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format.”).

The proposed rule would require that the following statement follow the summary of adverse reactions: “These are not all the possible side effects of [Insert Drug Name]. Call your health care provider if you have side effects that worsen or do not go away. You may also report side effects to FDA at [insert current FDA telephone number and web address for voluntary reporting of adverse reactions]” (see proposed § 208.40(c)(3)). Including information in PMI about how to report side effects to FDA is consistent with our efforts to encourage patients and healthcare providers to report suspected adverse reactions to FDA.

Under the heading “Directions for Use,” the proposed rule would require the statement “Use exactly as prescribed” to appear first after the heading to emphasize the importance of taking the prescription drug product as directed by the healthcare provider (see proposed § 208.40(c)(4)). We propose that the statement “Use exactly as prescribed” must be followed by a summary of how the prescription drug product must be administered and the route of administration. This section of PMI would also contain basic directions for use and any special instructions on how to administer the drug (for example, whether it should be taken with food or taken at a period of time before or after eating certain foods, or what to do if a patient misses a scheduled dose). If applicable, this section would include a statement of special handling, storage conditions, and disposal information. The dosing and administration and the storage, handling, and disposal information must be consistent with the most relevant information to patients that is found: (1) in the “DOSAGE AND ADMINISTRATION” section of the PI and (2) in the “HOW SUPPLIED/STORAGE AND HANDLING” section for drug labeling that must meet the format and content requirements of §§ 201.56(d) and 201.57 or the “HOW SUPPLIED” section for drug labeling that must meet the format and content requirements of § 201.80.

We intend that detailed instructions for patients' use of drug products, known as “Instructions for Use,” will continue to be available as a separate document and approved by FDA, where

appropriate, for drug products with complicated administration instruction (for example, inhalers or injectables). We propose that PMI would direct patients to the FDA-approved Instructions for Use, when applicable.

G. Development of Patient Medication Information for New Drug Applications, Biologics License Applications, and Abbreviated New Drug Applications (Proposed § 208.50)

The proposed rule would require the applicant of an NDA or a BLA for a prescription drug product used, dispensed, or administered on an outpatient basis to create PMI (see proposed § 208.50(a)). PMI would be required for NDAs and BLAs pending or submitted on or after the effective date of the final rule, based on this proposed rule, and NDAs and BLAs that were approved by FDA before the effective date of the final rule, pursuant to the implementation schedule described in section V.J of this document. In certain circumstances, FDA may require more than one PMI for a prescription drug product, associated with a single PI, when one PMI cannot adequately convey the safe and effective use of the drug to patients. This may occur in instances where there are two or more formulations of a prescription drug product described in a PI. For example, more than one PMI would be needed where a product with a single PI has both an injection form and a pill form and the patient would benefit from separate PMI for the respective forms.

The proposed rule would require PMI for a prescription drug product approved or submitted for approval as an ANDA under section 505(j) of the FD&C Act that refers to a listed drug approved under section 505(c) of the FD&C Act for which FDA has approved PMI (see proposed § 208.50(b)(1)). The PMI for these ANDAs would be the same as the PMI approved for the RLD upon which its approval is based except for changes required: (1) because of differences approved under a suitability petition (see 505(j)(2)(C) of the FD&C Act and § 314.93 (21 CFR 314.93)) or (2) because the drug product and the reference listed drug are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv)).

The proposed rule would also require PMI for a prescription drug product approved or submitted for approval as an ANDA under section 505(j) of the FD&C Act that refers to a listed drug approved under section 505(c) of the FD&C Act for which approval of the RLD has been voluntarily withdrawn and the approval of the RLD is

withdrawn before the approval of PMI for the RLD (see proposed § 208.50(b)(2)). However, due to limitations of 505(j) of the FD&C Act and to ensure that all ANDAs that refer to an RLD have the same PMI, FDA would create a PMI template for these ANDAs. Except for permissible differences consistent with § 314.93 and § 314.94(a)(8)(iv), the PMI for these ANDAs would be the same as the content in the PMI template created by FDA.

FDA recognizes that there is a class of ANDAs that was approved under section 505(c) prior to the 1984 Hatch-Waxman Amendments to the FD&C Act. These pre-Hatch-Waxman ANDAs could be for products that are duplicates of a pre-1962 innovator drug product(s) that was subject to the Drug Efficacy Study Implementation (DESI) review and listed in a DESI notice, or they could be for similar or related products. These pre-Hatch-Waxman ANDAs did not rely on a specific listed drug as their basis of submission, but instead relied on the evidence of effectiveness that had been provided, reviewed, and accepted during the DESI process. The safety of these drugs had been determined on the basis of information included in the innovator new drug application(s) submitted prior to 1962 and by the subsequent marketing experience with the drug(s). In some circumstances these ANDAs have been treated similarly to ANDAs approved under section 505(j) of the FD&C Act in that they have followed changes in labeling made by the innovator product that was the subject of the DESI notice they relied on as their basis of submission. In other cases, some products have been treated similarly to other products approved under section 505(c) of the FD&C Act and have labeling that differs from the innovator product that was the subject of the DESI notice. In many cases, the innovator product(s) listed in the DESI notices are no longer marketed. FDA currently expects to address these ANDAs in the final rule in a similar manner as ANDAs approved under section 505(j) of the FD&C Act by requiring PMI for drugs covered by these ANDAs that either follows PMI created by an innovator drug product listed in the DESI notice they relied on as their basis of submission or, in appropriate circumstances, that follows a template created by FDA. FDA asks for comments on this proposal for this class of ANDAs.

H. Submission of Patient Medication Information for New Drug Applications, Biologics License Applications, and Abbreviated New Drug Applications (Proposed § 208.60)

The proposed rule would require NDA or BLA applicants (as described in this proposed rule) to submit PMI, along with the PI upon which the PMI is based, to FDA for approval (see proposed § 208.60(a)). For NDAs and BLAs submitted on or after the effective date of the final rule based on this proposed rule, PMI would be submitted as part of the application. For NDAs and BLAs approved before the effective date of the final rule or pending when the final rule becomes effective, the applicant would submit PMI to FDA in a prior approval supplement pursuant to § 314.70(b)(2)(v)(B) and § 601.12 or as an amendment as applicable. Section V.J of this document further explains when applicants would submit PMI to FDA for approval.

The proposed rule would also require ANDA applicants to submit PMI to FDA for approval after either: (1) PMI for the RLD is approved or (2) FDA has finalized the PMI template and provides notice of the template to the applicant, whichever applies (see proposed § 208.60(b)). Applicants of ANDAs submitted on or after the effective date of the final rule that rely on an RLD with an approved PMI or for which FDA has created a PMI template would be required to submit PMI to FDA as a part of the original ANDA. At the time the final rule becomes effective, applicants of pending ANDAs that reference an RLD for which there is no PMI will be required to submit an amendment once PMI is available for the RLD or once FDA has created a PMI template, if this occurs before the ANDA is approved. Applicants of ANDAs approved before the effective date of the final rule or before PMI is approved for their RLD or before FDA makes a template available, as applicable, would be required to submit a supplement with PMI to FDA, consistent with § 314.70. Generally, applicants would submit a supplement to FDA with PMI that is the same as that for the RLD or FDA-created template except for changes required: (1) because of differences approved under a suitability petition (see 505(j)(2)(C) of the FD&C Act and § 314.93) or (2) because the drug product and the reference listed drug are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv)).

I. Providing Patient Medication Information to Patients (Proposed § 208.70)

Proposed § 208.70(a) would require authorized dispensers to provide FDA-approved PMI to patients (or their agents) every time a prescription drug product is used, dispensed, or administered on an outpatient basis when such PMI is available. Providing PMI when the prescription drug product is used, dispensed, or administered on an outpatient basis will help remind and reinforce for the patient the essential information the patient needs to know about the prescription drug product and the basic directions on how to use the product. This will also ensure that patients receive any updated information about their prescription drug product when it is available. It is not anticipated that PMI would be provided each and every time a prescription drug is used (for example,

every time a patient is provided with a pill or capsule from a prescription) or administered (for example, each time a cream is applied), but rather the first time the prescription is used, dispensed, or administered and each time a prescription is dispensed (for example, when a prescription is refilled). Although authorized dispensers would be required to always have PMI available in paper format, this proposed rule is flexible in terms of distribution mechanisms. This proposed rule would allow for electronic distribution (in addition to paper format) and accommodates for future technological advances in providing PMI to patients.

Section 510 of the FD&C Act requires all persons engaged in manufacturing, preparing, issuing, compounding, or processing a drug to register with FDA and provide us with a list of drug products in commercial distribution. Under section 510(g)(1) of the FD&C Act, however, certain pharmacies are

exempt from such registration and listing requirements. The distribution of PMI by a pharmacy does not limit this exemption. Accordingly, under proposed § 208.70(b), an authorized dispenser would not be subject to the registration and listing requirements under section 510 of the FD&C Act solely because of an action performed by the authorized dispenser to comply with this proposed rule.

J. Schedule for Implementing the General Requirements for Patient Medication Information (Proposed § 208.80)

1. Implementation Schedule for Applicants To Submit PMI to FDA for NDAs, BLAs, or Efficacy Supplements

FDA is proposing a 5-year implementation schedule for PMI. The proposed implementation schedule for PMI is summarized in table 1 of this document.

TABLE 1—IMPLEMENTATION SCHEDULE

NDAs, BLAs, and efficacy supplements	Time by which PMI must be submitted to FDA
Applications submitted on or after the effective date of the final rule ¹	Time of submission (part of application).
Applications pending at the time of the effective date of the final rule	No later than 1 year after the date of approval of the pending application.
Applications approved on or before the effective date and that have a Medication Guide required under part 208 or a PPI required under § 310.501 or § 310.515.	No later than 1 year after the effective date of the final rule.
Applications approved from January 1, 2013, up to and including the effective date of the final rule that do not have a Medication Guide required under part 208 or a PPI required under § 310.501 or § 310.515.	No later than 2 years after the effective date of the final rule.
Applications approved from January 1, 2008, up to and including December 31, 2012, that do not have a Medication Guide required under part 208 or a PPI required under § 310.501 or § 310.515.	No later than 3 years after the effective date of the final rule.
Applications approved from January 1, 2003, up to and including December 31, 2007, that do not have a Medication Guide required under part 208 or a PPI required under § 310.501 or § 310.515.	No later than 4 years after the effective date of the final rule.
Applications approved on or before December 31, 2002, that do not have a Medication Guide required under part 208 or a PPI required under § 310.501 or § 310.515.	No later than 5 years after the effective date of the final rule.

¹ Final rule refers to a final rule that may publish based on this proposed rule.

The proposed rule would require a staggered implementation schedule for applicants to submit PMI to FDA for NDAs, BLAs, and efficacy supplements (see proposed § 208.80(a)). As indicated in table 1 of this document, for the purposes of this rule, the time by which applicants would be required to submit PMI to FDA would primarily be based on when the NDA, BLA, or efficacy supplement was approved. If an NDA or a BLA has one or more approved efficacy supplements, the approval date of the efficacy supplement that triggers the earliest PMI submission would be used to determine the submission date. We propose that the final rule based on this proposed rule become effective 6 months after the date of publication in the **Federal Register**. The proposed rule would require applicants of NDAs, BLAs, or efficacy supplements submitted for approval on or after the effective date of the final rule to include PMI as part of the application submitted to FDA (see proposed § 208.80(a)(1)).

The proposed rule would require the applicants of NDAs, BLAs, or efficacy supplements pending on the effective date of the final rule to submit PMI to FDA no later than 1 year after the date of approval of the pending application (see proposed § 208.80(a)(2)). A pending application's approval would not be delayed because of the new requirements for PMI.

The implementation schedule in proposed § 208.80(a)(3) would require applicants of NDAs and BLAs that have a current FDA-approved Medication Guide required under part 208 or an FDA-approved PPI required under §§ 310.501 or 310.515 to submit PMI to FDA no later than 1 year after the effective date of the final rule. Because these prescription drug products already have approved patient labeling, FDA believes that 1 year will be sufficient to convert the existing FDA-approved Medication Guide and FDA-approved required PPIs to meet the requirements of the final rule. This proposed rule

does not modify or affect the REMS requirements. As previously discussed in sections V.A and V.B of this document, once a prescription drug product has FDA-approved PMI, the current requirements for Medication Guides and PPIs would no longer be applicable to such product.

Apart from applications that have an existing FDA-approved Medication Guide or FDA-approved PPI, the implementation schedule proposed in § 208.80(a)(4) through (a)(7) would generally require applicants to submit PMI for newer products first, followed by older products. Newer prescription drug products would generally have PMI at the earliest possible date because these prescription drug products may be less familiar to patients. Staggering the PMI implementation is intended to provide applicants with sufficient time to create PMI and submit it to FDA and would also allow FDA to best use our resources to approve PMI efficiently.

2. Implementation Schedule for Applicants To Submit PMI to FDA for ANDAs

The labeling for the ANDA drug product must be the same as the labeling for its RLD at the time of the ANDA's approval, as required in § 314.94(a)(8)), except for changes required: (1) because of differences approved under a suitability petition (see 505(j)(2)(C) of the FD&C Act and § 314.93) or (2) because the drug product and the reference listed drug are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv)). Therefore, the proposed rule would require that applicants for which an ANDA is submitted for approval on or after the effective date of the final rule must submit PMI to FDA as part of the application if the PMI for the RLD is approved at the time the ANDA is submitted, or if FDA has finalized the PMI template and provided notice of the template to the applicant (see proposed § 208.80(b)(1)(i)). If PMI for the RLD is not approved or if FDA has not finalized the PMI template and provided notice of the template to the applicant, whichever applies, at the time the ANDA is submitted but such PMI is approved for the RLD or FDA finalizes the template and provides notice of the template to the applicant before the ANDA is approved, the applicant for the ANDA must submit PMI in an amendment to the pending application after the approval of the PMI for the RLD or after FDA finalizes the PMI template and provides notice of the template to the applicant, whichever applies (see proposed § 208.80(b)(1)(ii)). If PMI is approved for the RLD or if FDA finalizes the PMI template and provides notice of the template to the applicant after the ANDA is approved, the applicant must submit a supplement with the PMI consistent with § 314.70, after the approval of the PMI for the RLD or after FDA finalizes the PMI template and provides notice of the template to the applicant, whichever applies (see proposed § 208.80(b)(1)(iii)).

For ANDAs pending on the effective date of the final rule, the proposed rule would require applicants to submit an amendment with PMI if the PMI for the RLD is approved or if FDA finalizes the PMI template and provides notice of the template to the applicant, whichever applies, before the ANDA is approved (see proposed § 208.80(b)(2)(i)). If PMI for the RLD is approved or if FDA finalizes the PMI template and provides notice of the template to the applicant after the pending ANDA is approved,

the ANDA applicant must submit a supplement with PMI to FDA consistent with § 314.70, after the approval of the PMI for the RLD or after FDA finalizes the PMI template and provides notice of the template to the applicant, whichever applies (see proposed § 208.80(b)(2)(ii)).

The proposed rule would require applicants of ANDAs approved on or before the effective date of the final rule to submit a supplement with a PMI package, consistent with § 314.70.

3. Implementation Schedule for Authorized Dispensers To Provide PMI to Patients

The proposed rule would require authorized dispensers to provide FDA-approved PMI, when such PMI is available, beginning 2 years after the effective date of a final rule based on this proposed rule (see proposed § 208.80(c)). Dispensers should check the FDA labeling repository at <https://labels.fda.gov> on a monthly basis for newly FDA-approved PMI or revised PMI. It is understood that dispensers may need a reasonable amount of time to download PMI after it is published; however, it is expected that they will update their systems on a monthly basis.

Although only a small percentage of prescription drug products would have approved PMI 2 years after the effective date of the final rule, most prescription drug products that previously had Medication Guides would have FDA-approved PMI at that point. Once FDA approves PMI for a prescription drug product that previously had a Medication Guide, dispensers would no longer need to follow the requirements for providing the Medication Guide under proposed § 208.96 (see current § 208.24).

K. Waivers (Proposed § 208.90)

The proposed rule would allow for waivers from one or more of the proposed requirements for PMI (for example, the format and content of PMI and submitting and distributing PMI) if we determine that any requirement is inapplicable, unnecessary, impracticable, or contrary to patients' best interests for a particular prescription drug product (see proposed § 208.90). Waivers could be initiated by FDA or requested by a person or entity that is covered by the final rule. FDA may consider an applicant's request for an extension from the specified implementation date to fully comply with the PMI requirements. Such requests will be evaluated on a case-by-case basis.

As an example, FDA proposes that a waiver or extension would be

considered if FDA determined that complying with the requirements for PMI could contribute to a drug shortage or otherwise prevent patient access to the drug product.

As another example, FDA proposes that a waiver or extension would be considered if the CDC plans to use its delegated authority to develop and issue emergency use instructions for eligible medical countermeasures under section 564A(e) of the FD&C Act (21 U.S.C. 360bbb-3a(e)).

FDA considers the one-page requirement to be a key feature of PMI. We envision rarely granting a waiver to the one-page requirement (see proposed § 208.30(a)(2)). However, we may allow PMI to exceed one page, if necessary, for the safe and effective use of the prescription drug product.

FDA is seeking comment on possible PMI requirements for which waivers could be requested and the criteria that FDA might consider when evaluating such requests. Waivers or extensions requested by a person or entity covered by the final rule will be reviewed on a case-by-case basis. Requests for waivers or extensions and the rationale for the waiver or extension for PMI requirements for NDAs and BLAs would need to be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product. For ANDAs, the requests for waivers or extensions and the rationale for the waiver or extension would need to be submitted to the Director of the Office of Generic Drugs. For biological products, requests for waivers or extensions and the rationale for the waiver or extension would be submitted to the FDA application division in the office with product responsibility.

L. Medication Guides: Patient Medication Information for Blood and Blood Components Intended for Transfusion (Proposed § 606.123)

When finalized, this proposed rule would add proposed § 606.123 (Medication Guides: Patient Medication Information for blood and blood components intended for transfusion). The addition of the proposed requirement would ensure that every patient who receives blood or a blood component on an outpatient basis receives PMI.

The proposed rule would require establishments that collect blood and blood components for transfusion to create PMI, as described in proposed part 208, for distribution to the transfusion service (see proposed § 606.123(a)). The proposed rule would

require licensed blood establishments to submit PMI to FDA for approval.

The proposed rule would require transfusion services, as an authorized dispenser, to provide PMI to each patient (or the patient's agent) when blood or blood components are administered on an outpatient basis when such PMI is available (see proposed § 606.123(b)). Although the transfusion service must always have PMI available in paper format, the proposed rule is flexible in terms of distribution mechanisms. This proposed rule would allow for electronic distribution upon request and accommodates future technological advances in providing PMI to patients.

The proposed rule would allow for waivers from one or more of the proposed requirements for PMI (for example, the format and content of PMI, submitting, and distributing PMI) if we determine that any requirement is inapplicable, unnecessary, impracticable, or contrary to patients' best interests (see proposed § 606.123(c)). Waivers could be initiated by FDA or requested by a blood collection establishment or transfusion service. Requests for waivers or extensions and the rationale for the waiver or extension must be submitted to the FDA application division in the office with product responsibility. FDA is seeking comment on possible PMI requirements for which waivers would be requested and the nature of such requests.

In contrast to other prescription drug products, blood and blood components intended for transfusion are subject to the labeling requirements under §§ 606.121 and 606.122, including the requirement that a circular of information for prescribers be made available for distribution. We currently recognize a circular of information prepared jointly by the AABB (formerly known as the American Association of Blood Banks), the American Red Cross, America's Blood Centers, and the Armed Services Blood Program as acceptable.

We specifically invite public comments on the following topics with respect to PMI for blood and blood components:

1. Informational materials that are currently available to patients who receive blood or blood components for transfusion on an outpatient basis, including the adequacy of such information.

2. The difference in the proposed requirements for applicants that FDA should consider in finalizing the rule (*i.e.*, the requirement to submit PMI to FDA for approval).

3. The feasibility of industry jointly developing PMI documents for blood and blood components intended for transfusion on an outpatient basis and the timeframe needed to develop the documents.

4. The electronic storage of PMI for blood and blood components on the FDA website <https://labels.fda.gov>.

We also request public comments on the feasibility of blood transfusion services, as the authorized dispenser of blood and blood components, providing PMI to patients (or patients' agents) who are administered blood or blood components on an outpatient basis.

At this time, we are not proposing an implementation schedule for blood collection establishments to develop PMI and for applicants to submit it to FDA for approval. We propose that the final rule may include staggered implementation schedules for blood collection establishments and transfusion services because of the need to explore the feasibility of industry jointly developing PMI documents.

VI. Electronic Repository for Patient Medication Information

PMI for prescription drug products would be stored electronically in the FDA labeling repository at <https://labels.fda.gov> that currently holds PI, FDA-approved patient labeling, and carton and container labeling submitted to us under current requirements, such as labeling, listing information, and annual reports. PMI for blood and blood components will either be stored electronically in the FDA labeling repository (<https://labels.fda.gov>) or a link will be provided at <https://labels.fda.gov> to the site where they are stored electronically. The FDA labeling repository is searchable by proprietary name (if any), active ingredient, company name, National Drug Code number, application number or regulatory citation, and proprietary name and company. The labeling found in the repository will be compliant with section 508 of The Rehabilitation Act of 1973 requirements, which can help to provide broader access to patients.

The purpose of the electronic repository would be to provide a single online electronic data source that allows easy open access to PMI. Maintaining PMI in an electronic format would allow patients, healthcare providers, and pharmacies open access to up-to-date PMI.

VII. Proposed Effective Date

We propose that a final rule based on this proposed rule become effective 6 months after the date the final rule publishes in the **Federal Register**. Given

the number of prescription drug products that will be impacted by this proposed rule, the constraints on our resources, and the need to provide applicants with sufficient time to create PMI and submit it to FDA, we understand that 6 months is not likely to be sufficient time to fully implement this rule. Thus, we are proposing to follow the implementation plan set out in section V.J of this document.

VIII. Preliminary Economic Analysis of Impacts

We have 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 us 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). The Office of Information and Regulatory Affairs has determined that this proposed rule is a significant regulatory action as defined by Executive Order 12866, section 3(f)(1).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we find the cost of the proposed rule to be a substantial percentage of sales for small businesses, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to 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 \$177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

A. Summary of Costs and Benefits

This proposed rule would require that human prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an

outpatient setting, be accompanied by a one-page product information document, or Medication Guide, known as Patient Medication Information (PMI). Manufacturers of these products would be required to create PMI according to standardized content and format requirements. PMI would be reviewed and approved by FDA and stored in an online, central repository accessible to the public. Firms would incur costs to develop PMI. FDA would incur costs to review PMI as well as to establish and maintain the online database. For a small subset of drug products, FDA would also incur costs to develop a template for PMI. Dispensers may face additional costs to print and distribute PMI. Firms that currently supply Consumer Medication Information (CMI) to pharmacies may also incur costs associated with switching from CMI to PMI. PMI would provide the public with FDA-approved labeling that is created specifically for patients. The public would benefit from this labeling with decreased search costs for information. The public may also benefit from a reduction in risk associated with their drug products, including blood and blood component products transfused in outpatient settings, due to the availability of PMI if the new labeling helps patients make better healthcare decisions.

In our primary analysis, we assume that all products subject to the rule would stay on the market. However, we

observe that the costs of creating, updating, or submitting PMI could exceed the profits for certain low-revenue drug products. Some of these products would be eligible for a waiver or extension of the requirements of PMI, for example, if complying with the requirements could contribute to a drug shortage or otherwise impede patient access. For those products not eligible for a waiver or extension, firms may choose to discontinue marketing the drugs, which would lead to additional social costs under the proposed rule. We perform additional analyses to better understand how the costs and benefits of the rule would be affected by waivers and extensions or discontinuations of drug products.

The costs and benefits of the proposed rule are summarized in table 2. This table shows the estimated average annualized net costs of this rule, using both 7 and 3 percent annual discount rates over a 10-year evaluation period. We estimate that the present value of net costs over 10 years would range from \$105.0 to \$312.5 million, with a primary estimate of \$192.8 million, at a 3 percent discount rate and from \$89.0 to \$263.6 million, with a primary estimate of \$162.6 million, at a 7 percent discount rate. Annualizing these costs over 10 years, we estimate the cost would range from \$12.3 to \$36.6 million per year at a 3 percent discount rate, with a primary estimate of \$22.6 million per year, and from \$12.7 to \$37.5

million per year using a discount rate of 7 percent, with a primary estimate of \$23.2 million.

Table 2 also shows the estimated annualized benefits and other non-quantified benefits. The monetized benefit of this rule would result from decreased search costs for information pertaining to drug, blood, and blood component products received in outpatient settings. We estimate that the present discounted value of these potential benefits from PMI over 10 years would range between \$127.5 million and \$4.3 billion using a 3 percent discount rate, with a primary estimate of \$1.6 billion; using a 7 percent discount rate, the present-value benefits from PMI would range between \$101.0 million and \$3.4 billion, with a primary estimate of \$1.3 billion. Annualized over 10 years, we estimate that the benefit from PMI would range between \$14.9 and \$507.9 million per year, with a primary estimate of \$188.0 million, using a 3 percent discount rate; with a 7 percent discount rate, we estimate the annualized benefit to range between \$14.4 and \$486.8 million, with a primary estimate of \$180.5 million per year. In addition to these monetized benefits, patients may experience a reduction in risk associated with drug, blood, and blood component products if PMI leads them to make better, more informed healthcare decisions.

TABLE 2—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized Monetized \$m/year	\$180.5 188.0	\$14.4 14.9	\$486.8 507.9	2020 2020	7 3	10 10	
Annualized Quantified	7 3	
Qualitative	Risk reduction from improved access to information.						
Costs:							
Annualized Monetized \$m/year	23.2 22.6	12.7 12.3	37.5 36.6	2020 2020	7 3	10 10	
Annualized Quantified	7 3	
Qualitative							
Transfers:							
Federal Annualized Monetized \$m/year	7 3	
From/To	From:			To:			
Other Annualized Monetized \$m/year	7 3	
From/To	From:			To:			

Effects:
 State, Local or Tribal Government: No effect.
 Small Business: Potential for significant impact on the smallest firms.

TABLE 2—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE—Continued

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Wages: No effect. Growth: No effect.							

In calculating the costs discussed above, we have netted out the cost savings that would stem from this proposed rule. PMI would replace the current Medication Guides and Patient Package Inserts; therefore, manufacturers would not need to create or submit updates to their Medication Guides and Patient Package Inserts, which would result in cost savings to those manufacturers.

B. Summary of Regulatory Flexibility Analysis

To determine the impact of the proposed rule on small entities that manufacture reference drug products, we compare the cost of the rule to the total U.S. sales, as reported by Dun and Bradstreet, of the small entities. For all such firms with 1,000 or fewer employees, we estimate the average cost of PMI to range between 0.2 and 1.0 percent of sales. The largest impact would be felt by the smallest firms; for firms with one to five employees, we estimate that the cost of PMI would range between 1.4 and 7.1 percent of sales. To determine the impact of the proposed rule on small entities that manufacture non-reference drug products, we estimate the average annualized cost of PMI and compare that to the firms' estimated receipts by firm size. For firms that manufacture non-reference products with 499 or fewer employees, we estimate the average cost of PMI to range between 0.02 and 0.05 percent of receipts. The largest impact would again be felt by the smallest firms; for such firms with 1 to 19 employees, we estimate the average cost of PMI would range between 0.04 and 0.10 percent of receipts. To determine the impact of the proposed rule on small entities that manufacture blood and blood component products for transfusion in an outpatient setting, we estimate the average annualized cost of PMI and compare that to the sales data for U.S. firms obtained from Dun and Bradstreet. We estimate that the annualized cost of PMI would represent less than one tenth of a percent of annual sales under any cost or discounting scenario for these firms. Given that we find the cost of the proposed rule to be a substantial

percentage of sales for small businesses that manufacture drug products, the Agency concludes that this rule, if finalized, would have a significant adverse impact on a substantial number of small entities.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 48) and at <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.

IX. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) 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.

X. 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. 3501–3521). A description of these provisions is given in the *Description* section of this document with an estimate of the annual reporting and third-party disclosure, including an estimate of the one-time reporting and one-time third-party disclosure. 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.

FDA invites 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: Medication Guides: Patient Medication Information (part 208)—OMB Control Number 0910–0393—Revision.

Description: We are proposing to amend our regulations governing human prescription drug product labeling. The proposed rule would revise part 208 concerning Medication Guides and part 606 for blood and blood components intended for transfusion. With certain exceptions, the proposed rule would require applicants to create a new type of Medication Guide, called PMI, for human prescription drug products (for the purposes of this proposed rule, a drug product also includes a biological product licensed under section 351(a) and (k) of the PHS Act), used, dispensed, or administered on an outpatient basis. Blood establishments would also be required to create PMI for blood and blood components intended for transfusion administered on an outpatient basis. The goal of the proposed rule is to improve public health by providing clear, concise, accessible, and useful written prescription drug product information available in a consistent and easily understood format to help patients use their prescription drug products safely and effectively.

Patients need prescription drug product information that is clear, concise, and consumer-friendly. To improve how patients receive prescription drug product information, we are proposing to require that applicants of human prescription drug products used, dispensed, or administered on an outpatient basis and establishments that collect blood and blood components transfused in an outpatient setting create PMI in a one-page document with standardized format and content. All PMI would be based on and consistent with the PI and the labeling requirements under §§ 201.56, 201.57, 201.80, and 606.122. Additionally, PMI in electronic format would need to be printable and identical to PMI in paper format.

Applicants of NDAs and BLAs would be required to create PMI and submit it

to FDA for approval. While all blood establishments would be required to create PMI, only licensed establishments would be required to submit PMI to FDA. The proposed rule covers NDAs including 505(b)(1) and (2) applications and BLAs including interchangeable biosimilars and non-interchangeable biosimilars. Additional information to help with drafting biosimilar labeling is available in the final guidance for industry entitled "Labeling for Biosimilar Products" (available at <https://www.fda.gov/media/96894/download>). Any specific recommendations for labeling for interchangeable products will be provided in future guidance. We invite comments on whether interchangeable products would have to have their own PMI or whether they would copy the PMI of the reference product to which they would be interchangeable.

Applicants of ANDAs for a prescription drug product approved or submitted for approval that rely on an RLD with an FDA-approved PMI would be required to submit a PMI to FDA for approval. The PMI for these ANDAs would be the same as the PMI approved for the RLD upon which its approval is based, except for changes required or permissible differences pursuant to § 314.94(a)(8)(iv).

In addition, applicants of ANDAs that refer to a listed drug approved under section 505(c) of the FD&C Act for which approval has been voluntarily withdrawn before the approval of PMI for the RLD would be required to submit a PMI. However, because of the limitations of 505(j) of the FD&C Act and to ensure that all ANDAs that refer to an RLD have the same PMI, FDA would create a PMI template for these ANDAs. The PMI for these ANDAs would be the same as the PMI template that FDA created except for changes required or permissible differences pursuant to § 314.94(a)(8)(iv).

Description of Respondents: The respondents to this collection of information are applicants of NDAs and BLAs; applicants of ANDAs; and authorized dispensers of human prescription drug products used, dispensed, or administered on an outpatient basis, including authorized dispensers of transfusion services that provide blood or blood components for administration on an outpatient basis.

For the purposes of this analysis, we estimated the burden on applicants of ANDAs by estimating the number of ANDA products that reference an NDA RLD.

There are five human blood and blood component products intended for

transfusion that could be administered on an outpatient basis that would need PMI: (1) whole blood, (2) red blood cells, (3) platelets, (4) plasma, and (5) cryoprecipitate antithemophilic factor. Based on past experience with development of information available for distribution with blood and blood components for transfusion (for example, circular of information), FDA assumes that a single PMI document would be developed for each blood or blood component. Thus, for the purposes of this analysis, FDA assumes that five PMI documents would be created initially for human blood and blood component products and considers this as part of the estimate for BLAs.

We estimate the burden associated with this collection of information as follows:

One-Time Burdens

If the proposed rule is finalized, it will impose a one-time burden for respondents with regard to both reporting and third-party disclosure. To minimize this burden on respondents, FDA is proposing a 5-year implementation schedule as shown in table 3 of this document that is proposed to be codified at § 208.80.

TABLE 3—ONE-TIME BURDEN ¹

21 CFR section and activity	Years in which burden occurs after the effective date of the final rule	Number of respondents	Number of responses per respondent	Total responses	Average burden per response	Total hours
One-Time Reporting for Applicants of Existing and Pending NDAs and BLAs To Create and Submit PMI To FDA						
PMI for NDAs and BLAs Submitted Under §§ 314.70 and 601.12 (NDAs and BLAs approved on or before the effective date of the final rule based on this proposed rule) (§§ 208.50 and 208.60, and 606.123(a)).	Year 1	1,669	0.32	529	320	169,280
	Year 2	1,669	0.32	529	320	169,280
	Year 3	1,669	0.32	529	320	169,280
	Year 4	1,669	0.32	529	320	169,280
	Year 5	1,669	0.32	528	320	168,960
	Subtotal
PMI for Pending NDAs and BLAs Submitted Under §§ 314.60 and 601.2 (NDAs and BLAs pending on the effective date of the final rule based on this proposed rule) (§§ 208.50 and 208.60, and 606.123(a)).	Year 1	7	1	7	320	2,240
	Subtotal	849,166
One-Time Reporting for Applicants of Existing and Pending ANDAs To Create and Submit PMI to FDA						
PMI for ANDAs Submitted Under § 314.97 (ANDAs approved on or before the effective date of the final rule based on this proposed rule) (§§ 208.50 and 208.60).	Year 1	840	1.48	1,240	27	33,480
	Year 2	840	1.48	1,240	27	33,480
	Year 3	840	1.48	1,240	27	33,480
	Year 4	840	1.48	1,240	27	33,480
	Year 5	840	1.48	1,240	27	33,480
	Subtotal
PMI for Pending ANDAs Submitted Under § 314.96 (ANDAs pending on the effective date of the final rule based on this proposed rule) (§§ 208.50 and 208.60).	Year 1	13	4.54	59	27	1,593
	Subtotal	168,993

TABLE 3—ONE-TIME BURDEN ¹—Continued

21 CFR section and activity	Years in which burden occurs after the effective date of the final rule	Number of respondents	Number of responses per respondent	Total responses	Average burden per response	Total hours
One-Time Reporting for Waivers for Applicants of NDAs, BLAs, and ANDAs Over a 5-Year Period						
Requests for Waiver (§§ 208.90 and 606.123(c))	Years 1 through 5.	76	1	76	4	304
One-Time Third-Party Disclosure						
Downloading and Integrating PMI §§ 208.70 and 606.123(b)	49,279	1	49,279	16	788,464
Total	1,806,927

¹ Numbers have been rounded to the nearest hundredth.

Applicants of NDAs and BLAs will incur a one-time regulatory burden for applications that are approved on or before or are pending on the effective date of the final rule based on this proposed rule associated with creating PMI and submitting PMI to FDA for approval as required under proposed §§ 208.50, 208.60, and 606.123(a). We also anticipate that applicants of ANDAs will incur a one-time regulatory burden associated with creating PMI and submitting PMI to FDA for approval as required under proposed §§ 208.50 and 208.60 for applications that are approved on or before or are pending on the effective date of the final rule. This one-time regulatory burden for all affected applicants with applications approved on or before the effective date would be distributed over a 5-year implementation period after the effective date of the final rule based on the proposed rule. The implementation schedule is shown in table 3 of this document and is proposed to be codified at § 208.80.

Proposed § 208.80(a) would require an implementation schedule for applicants of NDAs and BLAs approved on or before the effective date of the final rule (existing drug products) to submit PMI for applications on a staggered basis, beginning 1 year after the effective date of the final rule. The timeframe by which applicants would be required to submit PMI to FDA for approval would primarily be based on when the application or the application’s efficacy supplement was approved. Table 3 of this document provides an estimate of the one-time reporting burden for existing drug products associated with creating PMI and submitting PMI to FDA in a supplement. Based on information available in our establishment and product listing database for drug and biological products, we estimate that 1,669 applicants of NDAs and BLAs (1,453 NDA applicants + 216 BLA applicants)

will be affected by this proposed rule. Collectively, these respondents are responsible for submitting a labeling supplement with PMI for 2,644 existing drug products. The number of existing drug products was estimated based on an analysis of data from the Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations (available at <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>) and the Purple Book: Lists of Licensed Biological Products With Reference Products Exclusivity and Biosimilarity Interchangeability Evaluation (available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>) to determine the number of unique products on the market that are used primarily in outpatient settings. These applicants would submit a labeling supplement with PMI for approximately 528.8 products each year over a 5-year implementation period (a total of 2,644 products), beginning 1 year after the effective date of the final rule based on this proposed rule and continuing for 5 years (table 3 of this document).

Additionally, applicants of applications pending at the time the final rule becomes effective may need to amend their NDAs and BLAs to comply with the PMI requirements in proposed part 208. Based on our experience with labeling submissions, we have estimated that 5 percent of 134 NDAs and BLAs submitted under §§ 314.60 and 601.2 will be pending at the time the final rule based on this proposed rule becomes effective. Therefore, we assume that approximately seven applicants of NDAs and BLAs will submit amendments to their NDA or BLA to include PMI for seven pending applications on the effective date of the final rule (table 3 of this document).

Based on our experience with labeling submissions for medication guides and PPIs, we estimate that approximately 320 hours, on average, would be needed for applicants of NDAs and BLAs to create PMI and submit PMI to FDA for approval. This estimate subtotals 849,166 hours for applicants of NDAs and BLAs that are approved on or before or are pending on the effective date of the final rule (846,080 hours for NDAs and BLAs approved on or before the effective date of the final rule + 2,240 hours for NDAs and BLAs pending on the effective date of the final rule) (table 3 of this document).

Under proposed part 208, applicants of ANDAs approved on or before the effective date of the final rule (existing ANDAs) would be required to submit PMI to FDA in a supplement after the PMI is approved for the RLD product or after the PMI template that FDA created is provided, whichever applies. Table 3 of this document provides an estimate of the one-time reporting burden associated with existing ANDAs. Based on information available in our establishment and product listing database for drug and biological products, we estimate that 840 applicants of existing ANDAs will be affected by this proposed rule. Collectively, these respondents are responsible for submitting a labeling supplement with PMI for approximately 6,200 existing ANDAs (estimate based on data from the Orange Book from May 2018 of non-RLD ANDAs on the market) over a 5-year period, beginning 1 year after the effective date of the final rule based on this proposed rule and continuing for 5 years (approximately 1,240 per year).

Additionally, applicants of ANDAs pending at the time the final rule becomes effective would be required to submit PMI in an amendment after the PMI is approved for the RLD product or after the PMI template that FDA created is provided, whichever applies. Table 3

of this document provides an estimate of the one-time reporting burden associated with pending ANDAs. Using our experience with labeling submissions, we have estimated that 5 percent of the 1,186 ANDAs will be pending when the final rule based on this proposed rule becomes effective (59 pending ANDAs). We estimate that approximately 13 applicants of ANDAs will submit amendments to their ANDA to include PMI for 59 pending ANDAs.

Based on our experience with labeling and submissions, we estimate that approximately 27 hours, on average, would be needed for applicants of ANDAs to create PMI and submit PMI to FDA for approval. This estimate subtotals 168,993 hours for applicants of existing and pending ANDAs (167,400 hours for existing ANDAs + 1,593 for pending ANDAs) (table 3 of this document).

In some circumstances, an applicant may request or FDA may initiate a waiver under proposed § 208.90 or proposed § 606.123(c) of a PMI requirement, such as the content and format requirements. Based on our experience with labeling submissions, we estimate that 3 percent of the 2,529 applicants of existing and pending NDAs, BLAs, and ANDAs (1,669 applicants for existing NDAs and BLAs

+ 7 applicants of pending NDAs and BLAs + 840 applicants of existing ANDAs + 13 applicants of pending ANDAs) will request a waiver for a PMI requirement, approximately 76 applicants (table 3 of this document). We estimate that each applicant would submit one request, for a total of 76 requests. These requests would be submitted to us beginning 1 year after the effective date of the final rule and would be submitted throughout the 5-year implementation timeframe (table 3 of this document). The average burden per response is the estimated number of hours an applicant would spend creating and submitting the request to FDA. Based on our experience with labeling submissions, we estimate that approximately 4 hours, on average, would be needed per submission, subtotalling 304 hours (table 4 of this document).

To reduce the burden for authorized dispensers, FDA will submit PMI electronically for storage in a central repository. As a part of authorized dispensers' and transfusion services' normal business workflow, they will be able to download PMI from the central repository, integrate PMI into their existing software system, and provide PMI to patients as required under proposed §§ 208.70 and 606.123(b). As

such, authorized dispensers and transfusion services will incur a one-time burden to download and integrate PMI into their existing software system. While a healthcare provider can administer or provide a prescription drug product directly to a patient, FDA expects authorized dispensers will generally be pharmacists at retail pharmacies in most instances. Based on an analysis of pharmacy ownership and the number of owners with multiple pharmacies, we expect that 44,318 pharmacies could incur the burden associated with these activities. Additionally, we have estimated that 4,961 transfusion services will incur the burden associated with these activities, totaling 49,279 respondents for this burden. The average burden per recordkeeping is the estimated number of hours an authorized dispenser would spend downloading PMI into their existing software system. FDA estimates that approximately 16 hours would be needed to download and integrate PMI into the existing software system, totaling 788,464 hours (table 3 of this document).

Reporting

Table 4 shows the estimated annual reporting burden associated with this collection of information.

TABLE 4—ESTIMATED ANNUAL REPORTING BURDEN^{1 2}

21 CFR section and activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
PMI for NDAs and BLAs (§§ 208.50(a) and 208.60(a), and 606.123(a))	108	1.1	119	320	38,080
PMI for ANDAs (§ 208.50(b) and 208.60(b))	251	4.73	1,186	27	32,022
Waiver Requests for PMI requirements (§§ 208.90 and 606.123(c))	1,489	1	1,489	4	5,956
Medication Guides Submitted with NDAs and BLAs (§ 208.94 (previously § 208.20)) ..	57	1	57	320	18,240
Medication Guides Submitted as Supplements or Updates (§ 208.94 (previously § 208.26(a)))	108	1	108	72	7,776
Exemptions and Deferrals for Medication Guides (§ 208.98 (previously § 208.20))	1	1	1	4	4
Total					102,078

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.
² Numbers have been rounded to the nearest hundredth.

Under proposed §§ 208.50(a), 208.60(a), and 606.123(a), applicants of NDAs or BLAs would be required to create PMI and submit PMI to FDA as part of the respective application. Based on our review of the annual Prescription Drug User Fee Act performance reports from 1993 to 2014, we estimate that 108 applicants of NDAs and BLAs will submit an NDA under § 314.50 or a BLA under § 601.2 for 119 new drug products annually, on average. Based on our experience with the information collection, we estimate that this activity will require 320 hours per submission. We calculate, therefore, an annual

burden of 38,080 hours as reflected in table 4 of this document.

Under proposed §§ 208.50(b) and 208.60(b), applicants of ANDAs (new ANDAs) would be required to submit PMI to FDA as a part of the application. Accordingly, based on current data, we estimate that 251 ANDA applicants will submit PMI to FDA for approval, resulting in 1,186 submissions annually. Based on our experience with labeling submissions, we estimate that this activity will require an average of 27 hours per submission for a total of 32,022 hours annually as reflected in table 4 of this document.

Under proposed §§ 208.90 and 606.123(c), any covered entity may

submit a request for a waiver. Covered entities would include applicants and authorized dispensers. Based on our experience with labeling submissions, we estimate that 3 percent of the 359 applicants (108 NDA applicants and BLA applicants + 251 ANDA applicants) of new drug products and new ANDAs will request a waiver from a PMI requirement, approximately 11 applicants submitting 1 NDA, BLA, or ANDA each. The average burden per response is the estimated number of hours an applicant would spend creating and submitting the request to FDA. Based on our experience with labeling submissions, we estimate that

approximately 4 hours, on average, would be needed per submission, subtotalling 44 hours. Additionally, under proposed § 208.90, authorized dispensers and under proposed § 606.123(c) transfusion services may request a waiver for any requirement related to providing PMI to patients. Based on our experience with the information collection, we estimate that 1,478 authorized dispensers and transfusion services (3 percent of 49,279 authorized dispensers and transfusion services) will each request 1 waiver

from a PMI requirement. We estimate that the average burden per response is 4 hours. Therefore, we estimate that 1,489 covered entities/respondents (11 applicants of NDAs, BLAs, and ANDAs + 1,478 authorized dispensers and transfusion services) will request 1 waiver from a PMI requirement, totaling 5,956 hours (44 hours for NDA, BLA, or ANDA applicants + 5,912 hours for authorized dispensers and transfusion services), as reflected in table 4 of this document.

We propose to relocate current §§ 208.20 and 208.26(a) to proposed §§ 208.94 and 208.98. We have retained the estimates for current §§ 208.20 and 208.26(a) as previously approved by OMB under control number 0910–0393 as reflected in table 4 of this document.

Third-Party Disclosure

Table 5 shows the estimated annual third-party disclosure associated with this collection of information.

TABLE 5—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN^{1 2}

21 CFR section and activity	Number of respondents	Number of disclosures per respondent	Total annual disclosures	Average burden per disclosure	Total hours
Downloading PMI into Database (§§ 208.70 and 606.123(b))	49,276	12	591,312	0.5 (30 minutes)	295,656
Providing PMI to Patients (§§ 208.70 and 606.123(b))	93,697	45,924.63	4,303,000,000	0.02 (1 minute)	86,060,000
Medication Guide from Packer/Distributor to Authorized Dispenser (§ 208.96 (previously § 208.24(c))).	191	9,000	1,719,000	1.25	2,148,750
Medication Guide from Authorized Dispenser to Patient (§ 208.96 (previously § 208.24(e))).	88,736	5,705	506,238,880	0.05 (3 minutes)	25,311,944
Total					113,816,350

¹ There are no capital or operating and maintenance costs associated with this collection of information.
² Numbers have been rounded to the nearest hundredth.

Authorized dispensers, including transfusion services, would also be required to download updated PMI into their existing software system on a regular basis to ensure that patients receive the most up-to-date PMI. We anticipate that PMI would be updated in the central repository monthly. Therefore, authorized dispensers would need to download updated and new PMI from the central repository monthly. Consistent with our estimates to download and integrate PMI, we anticipate that 49,276 authorized dispensers could incur the burden associated with this activity. The average burden per recordkeeping is the estimated number of hours an authorized dispenser would spend downloading updated PMI into their existing software system. We estimate that 0.5 hours (30 minutes) would be needed to update PMI monthly, totaling 295,656 hours as reflected in table 5 of this document.

Proposed §§ 208.70(a) and 606.123(b) would require that authorized dispensers of human prescription drug products and transfusion services, respectively, provide FDA-approved PMI to patients when such PMI is available. Authorized dispensers and transfusion services must be capable of providing PMI in paper format to patients; however, they may provide PMI in electronic format to patients. Estimated printing costs will be equivalent to current printing costs, because dispensers already provide

written information in paper format to patients. Further, we do not expect that dispensers will incur additional costs when printing PMI, because the length of PMI will be shorter than written information currently provided to patients. Because providing prescription drug product information to patients is currently a part of authorized dispensers’ business practices and we are proposing that PMI be limited to one page, we anticipate time and effort for dispensers will be reduced.

Authorized dispensers and transfusion services may provide PMI in electronic format to patients when requested. Based on the normal course of their activities, many pharmacies may already have the contact information in patients’ profiles. As a result, dispensers could expeditiously provide patients with PMI electronically.

Based on current data, we estimate that 88,736 pharmacies and 4,961 transfusion services could be affected by proposed §§ 208.70 and 606.123(b), respectively. These respondents would be responsible for providing to patients PMI for human prescription drug products used, dispensed, or administered on an outpatient basis or when patients receive transfusions on an outpatient basis. Collectively, these respondents are responsible for dispensing 4.3 billion prescriptions annually and 3 million transfusions annually. We estimate that it will take dispensers an average of 0.02 hours (1 minute) to provide PMI to patients for

a total of 86,060,000 hours annually as reflected in table 5 of this document.

We propose to relocate current § 208.24(c) and (e) to proposed § 208.96. We have retained the estimates for current § 208.24(c) and (e) as previously approved under OMB control number 0910–0393 as reflected in table 5 of this document.

To ensure that comments on information collection are received, OMB recommends that written comments be submitted at <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting “Currently under Review—Open for Public Comments” or by using the search function. The title of this proposed collection is “Medication Guides: Patient Medication Information.” All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the **Federal Register**.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set

forth in Executive Order 13132. We have determined that this 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 conclude 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.

We are aware that States have laws or regulations that require pharmacists to counsel patients on the use of prescription drug products. We do not believe this proposed rule on PMI conflicts with such laws or regulations because this proposed rule would not affect any oral counseling requirements imposed by State laws or regulations. Nevertheless, we will continue to examine State laws for federalism purposes. We invite comments from interested persons, particularly with respect to State initiatives, to provide information to patients on prescription drug products used, dispensed, or administered on an outpatient basis.

XII. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the proposed rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 208

Labeling, Prescription drugs, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, 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 and under authority delegated to the Commissioner of Food and Drugs, the FDA proposes to amend 21 CFR parts 201, 208, 314, 606, and 610 as follows:

PART 201—LABELING

- 1. The authority citation for part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc–1, 360ee, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

- 2. In § 201.57, revise the last two sentences of paragraph (c)(18) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

* * * * *

(c) * * *

(18) * * * Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be provided to patients in compliance with §§ 208.70 and 208.96 of this chapter. Medication Guides for

distribution to patients are subject to the type size requirements set forth in §§ 208.30 and 208.94 of this chapter.

* * * * *

■ 3. In § 201.80, revise the last two sentences of paragraph (f)(2) to read as follows:

§ 201.80 Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

* * * * *

(f) * * *
(2) * * * Any FDA-approved patient labeling must be referenced in this section, and the full text of such patient labeling must be reprinted immediately following the last section of labeling or must accompany the prescription drug product labeling. The type size requirement for the Medication Guide set forth in §§ 208.30 and 208.94 of this chapter does not apply to the Medication Guide that is reprinted in or that accompanies the prescription drug product labeling unless such Medication Guide is to be detached and provided or distributed to patients in compliance with §§ 208.70 and 208.96 of this chapter.

* * * * *

■ 4. In § 201.100, add paragraph (g) to read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(g) When a Medication Guide is required under part 208 or § 606.123 of this chapter, the drug must have an approved Medication Guide and be dispensed with a Medication Guide (as described in part 208 or § 606.123 of this chapter).

■ 5. Revise part 208 to read as follows:

PART 208—MEDICATION GUIDES

Sec.

Subpart A—General Provisions for Patient Medication Information

208.10 Scope and purpose.
208.20 Definitions.

Subpart B—General Requirements for Patient Medication Information

208.30 Format of Patient Medication Information.
208.40 Content of Patient Medication Information.
208.50 Development of Patient Medication Information for new drug applications, biologics license applications, and abbreviated new drug applications.
208.60 Submission of Patient Medication Information for new drug applications, biologics license applications, and abbreviated new drug applications.
208.70 Providing Patient Medication Information to patients.

208.80 Schedule for implementing the general requirements for Patient Medication Information.

208.90 Waivers.

Subpart C—General Provisions for Medication Guides for Prescription Drug Products

208.91 Scope and purpose.
208.92 Definitions.

Subpart D—General Requirements for Medication Guides for Prescription Drug Products

208.94 Content and format of a Medication Guide.
208.96 Distributing and providing a Medication Guide.
208.98 Exemptions and deferrals.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360, 371, 374; 42 U.S.C. 262.

Subpart A—General Provisions for Patient Medication Information

§ 208.10 Scope and purpose.

(a) *Scope.* Subparts A and B of this part set forth requirements for patient labeling for prescription drug products used, dispensed, or administered on an outpatient basis. This patient labeling is a type of Medication Guide called Patient Medication Information. Any prescription drug product that is approved or submitted for approval under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)) and that is used, dispensed, or administered on an outpatient basis is required to have the Food and Drug Administration (FDA)-approved Patient Medication Information, with the exception of excluded entities identified in paragraph (d) of this section.

(b) *Purpose.* Patient Medication Information for prescription drug products required under this part provides concise, accessible, and useful written prescription drug product information for patients. Patient Medication Information must be delivered in a consistent and easily understood format to help patients use their prescription drug products safely and effectively.

(c) *Covered entities.* (1) Applicants of prescription drug products approved or submitted for approval under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)) must have FDA-approved Patient Medication Information for each prescription drug product used, dispensed, or administered on an outpatient basis, with the exception of excluded entities

identified in paragraph (d) of this section.

(2) Authorized dispensers are required to provide patients with FDA-approved Patient Medication Information each time a prescription drug product is used, dispensed, or administered on an outpatient basis when such Patient Medication Information exists.

(d) *Excluded entities.* Applicants of prescription drug products that are preventive vaccines that do not have a Medication Guide (as required under subparts C and D of this part) are not required to submit Patient Medication Information to FDA for approval for those products unless FDA determines that Patient Medication Information is required for safe and/or effective use of the product.

§ 208.20 Definitions.

The following definitions apply to this part:

Administered means the act of directly providing a prescription drug product to a patient by injection, inhalation, ingestion, application, or any other means by a licensed healthcare provider (or a licensed healthcare provider's agent) or by a patient (or a patient's agent) under the direction of a licensed healthcare provider (or a licensed healthcare provider's agent). In some circumstances, a product can be both administered and dispensed at the same time.

Applicant means all of the following:

(1) Any person who submits an application or abbreviated application or an amendment or supplement to their application under part 314 or part 601 of this chapter to obtain FDA approval of a new drug or biological product and,

(2) Any person who owns an approved application or an abbreviated application.

Authorized dispenser means an individual(s) or entity who is licensed, registered, or otherwise permitted by the jurisdiction in which the individual(s) or entity practices to provide prescription drug products in the course of professional practice.

Dispensed means the act of providing a prescription drug product to a patient (or a patient's agent) in either of the following ways:

(1) By a licensed healthcare provider (or a licensed healthcare provider's agent), either directly or indirectly, for administration by the patient (or the patient's agent) under or outside of the licensed healthcare provider's direct supervision.

(2) By an authorized dispenser (or an authorized dispenser's agent) under a

lawful prescription of a licensed healthcare provider.

Drug name means the proprietary name, if any, and the established name of the drug (as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(3)) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors.

Drug product means a finished dosage form (for example, tablet, capsule, solution), as defined in § 210.3 of this chapter, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. For the purposes of this part, *drug product* also includes a biological product licensed under section 351(a) and (k) of the Public Health Service Act (42 U.S.C. 262(a) and (k)).

Licensed healthcare provider means an individual who is licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

Manufacturer means all of the following:

(1) For a drug product that is not a biological product, the manufacturer as described in § 201.1 of this chapter.

(2) For a drug product that is a biological product, the manufacturer as described in § 600.3(t) of this chapter.

Patient means any individual to whom a drug product is intended to be or has been used, dispensed, or administered.

Patient Medication Information means a type of FDA-approved Medication Guide—a form of patient labeling—that conforms to the specifications set forth in subparts A and B of this part.

Revision date means the date (month/year) on which Patient Medication Information was initially approved or the date on which any changes have been made to the Patient Medication Information, whichever applies and whichever date is later.

Used (in relation to prescription drug products and Patient Medication Information) means the act of a patient (or a patient's agent) directly applying a prescription drug product to the body of the patient by injection, inhalation, ingestion, application, or any other means.

Subpart B—General Requirements for Patient Medication Information

§ 208.30 Format of Patient Medication Information.

(a) Patient Medication Information must meet the following requirements:

(1) Patient Medication Information must be written in English; provided, however, that in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English.

(2) Patient Medication Information provided to a patient in paper format must be legible and printed on a single side of an 8½ by 11-inch sheet of paper. It must not exceed a single page in length.

(3) Patient Medication Information provided in electronic format must be printable and produce a document that is identical to the Patient Medication Information in paper format.

(4) The required Patient Medication Information headings, subheadings, title “PATIENT MEDICATION INFORMATION,” and drug name(s), phonetic spelling of the drug name(s), dosage form(s), and route(s) of administration must appear in bold, beginning on the line immediately below the title.

(5) The title “PATIENT MEDICATION INFORMATION” must be presented in all uppercase letters. The proprietary name (if any) may be presented in all uppercase letters. Generally, no other words may be presented in all uppercase letters with the exception of commonly used acronyms.

(6) The title “PATIENT MEDICATION INFORMATION” and the drug name(s), phonetic spelling of the drug name(s), dosage form(s), and route(s) of administration beginning immediately below the title must appear centered at the top of the page.

(b) Patient Medication Information must *not* contain any of the following:

(1) Letter type that is less than 10-point font (1 point = 0.0138 inches) for any section of Patient Medication Information. However, the manufacturer's, packer's, and/or distributor's name and place of business (and the U.S. license number of the prescription drug product that is a biological product), the statement “The content of this Patient Medication Information has been approved by the U.S. Food and Drug Administration,” and the revision date can be less than 10-point font.

(2) Reverse type, lightface, shading, condensed type, or narrow fonts.

(3) Colors other than black type.

(4) Page number.

§ 208.40 Content of Patient Medication Information.

(a) *General content requirements for Patient Medication Information.* Patient

Medication Information must meet all general content requirements as follows:

(1) Patient Medication Information must be easily read and understood by the general population, including individuals with low literacy and comprehension levels.

(2) Patient Medication Information must not be promotional in tone.

(3) The content of Patient Medication Information must be scientifically accurate, must not be false or misleading in any particular, and must be based on and consistent with the Prescribing Information (PI) for the prescription drug product required under §§ 201.56, 201.57, 201.80, and 606.122 of this chapter and section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). Patient Medication Information for new drug applications and biologics license applications must be updated when new information becomes available that would cause the Patient Medication Information to become inaccurate, false, or misleading in accordance with §§ 314.70 and 601.12 of this chapter.

(4) The title “PATIENT MEDICATION INFORMATION” must appear at the top of the page.

(5) The drug name(s) must appear immediately below the title “PATIENT MEDICATION INFORMATION” and must include the phonetic spelling of the proprietary name, if any, and the established name (or the proper name) of the prescription drug product. The drug name(s) must be followed by the dosage form(s) and route(s) of administration. If the drug name needs to be used again throughout Patient Medication Information, only the proprietary name (if any) must be used. Those prescription drug products not having a proprietary name must use the established name or the proper name.

(6) The statement “The content of this Patient Medication Information has been approved by the U.S. Food and Drug Administration” must appear at the bottom of the page followed by the revision date.

(7) The name and place of business of the manufacturer, packer, or distributor of a prescription drug product that is not also a biological product must be included in Patient Medication Information below the statement required in paragraph (a)(6) of this section and the revision date. The licensed manufacturer's name, address, and U.S. license number of a prescription drug product that is also a biological product must be included in Patient Medication Information below the statement required in paragraph (a)(6) of this section and the revision date. The name and place of business of

the authorized dispenser may also be included in Patient Medication Information.

(8) Any heading, subheading, or specific information required under paragraphs (b) and (c) of this section that is inapplicable must be omitted from Patient Medication Information.

(b) *Required headings for Patient Medication Information.* Patient Medication Information must contain these headings in the following order if not omitted under paragraph (a)(8) of this section: [Insert drug name] is, Important Safety Information, Common Side Effects, Directions for Use.

(c) *Specific content required under headings for Patient Medication Information.* Each heading must contain the specific information as follows if not omitted under paragraph (a)(8) of this section:

(1) *[Insert drug name] is.* A concise summary of the outpatient indications and uses for the prescription drug product listed in the prescription drug product's Prescribing Information (PI). The information in this section would be consistent with the information found in the INDICATIONS AND USAGE section of the PI.

(2) *Important Safety Information.* This heading must contain these subheadings in the following order if not omitted under paragraph (a)(8) of this section:

(i) *Warnings.* A concise summary of serious warnings from the use of the prescription drug product, including any that may lead to death or serious injury. The *Warnings* subheading must include a summary of the information found in the prescription drug product's boxed warning, if any, that is most relevant for patients to know for the safe and effective use of the prescription drug product.

(ii) *Do not take.* A statement of the circumstances (if any) under which the prescription drug product should not be used because the risk of use outweighs any benefit. The information in the *Do not take* subheading would be consistent with the most relevant information to patients found in the CONTRAINDICATIONS section of the PI.

(iii) *Serious side effects.* A listing of the clinically significant adverse reactions or risks associated with the use of the prescription drug product that are most relevant to the patient, and information on when to call a healthcare provider or when and how to obtain emergency help if certain clinically significant adverse reactions occur. The information in the *Serious side effects* subheading must be consistent with either:

(A) The most relevant information to patients found in the "WARNINGS AND PRECAUTIONS" section for drug labeling that must meet the format and content requirements of §§ 201.56(d) and 201.57 of this chapter; or

(B) The "WARNINGS" section and the "PRECAUTIONS" section for drug labeling that must meet the format and content requirements of § 201.80 of this chapter.

(iv) *Tell your health care provider before taking.* A statement that identifies specific populations and conditions (if any) that may have clinically important differences in response to the prescription drug product or may change the recommendation for use of the prescription drug product.

(3) *Common Side Effects.* A statement of frequently occurring adverse reactions (if any) from the use of the prescription drug product, followed by the statement "These are not all of the possible side effects of [Insert Drug Name]. Call your health care provider if you have side effects that worsen or do not go away. You may also report side effects to FDA at [insert current FDA telephone number and web address for voluntary reporting of adverse reactions]."

(4) *Directions for Use.* The statement "Use exactly as prescribed" must appear first after this heading. This statement must be followed by how the prescription drug product must be administered and the route of administration. "Directions for Use" also must contain basic directions for use and any special instructions on how to administer the drug (for example, whether it should be taken with food or taken at a period of time before or after eating certain foods, or what to do if a patient misses a scheduled dose). If applicable, this section includes a statement of special handling, storage conditions, and disposal information. The dosing and administration and the storage, handling, and disposal information must be consistent with the most relevant information to patients found in:

(i) The "DOSAGE AND ADMINISTRATION" section of the PI; and

(ii) The "HOW SUPPLIED/STORAGE AND HANDLING" section for drug labeling that must meet the format and content requirements of §§ 201.56(d) and 201.57 of this chapter or the "HOW SUPPLIED" section for drug labeling that must meet the format and content requirements of § 201.80 of this chapter. Additional FDA-approved patient labeling must be referenced, when applicable.

§ 208.50 Development of Patient Medication Information for new drug applications, biologics license applications, and abbreviated new drug applications.

(a) *New drug applications and biologics license applications.* The applicant of a new drug application (NDA) or a biologics license application (BLA) for a prescription drug product used, dispensed, or administered on an outpatient basis must create Patient Medication Information in accordance with the requirements set forth in this part and other applicable regulations. In certain circumstances, FDA may require more than one Patient Medication Information for a prescription drug product, associated with a single PI, when one Patient Medication Information cannot adequately convey the safe and effective use of the drug to patients.

(b) *Abbreviated new drug applications.* (1) Except as provided in paragraph (b)(2) of this section, the applicant of a prescription drug product approved or submitted for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) must have Patient Medication Information that is the same as that of the reference listed drug upon which its approval is based except for:

(i) Changes required because of differences approved under a suitability petition (see 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and § 314.93 of this chapter); or

(ii) Changes permitted pursuant to § 314.94(a)(8)(iv) of this chapter.

(2) The applicant of a prescription drug product approved or submitted for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that refers to a listed drug approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c)) for which approval has been voluntarily withdrawn before the approval of the Patient Medication Information for the reference listed drug must have Patient Medication Information that is the same as that of the Patient Medication Information template that FDA creates for the prescription drug product except for:

(i) Changes required because of differences approved under a suitability petition (see 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and § 314.93 of this chapter); or

(ii) Changes permitted pursuant to § 314.94(a)(8)(iv) of this chapter.

§ 208.60 Submission of Patient Medication Information for new drug applications, biologics license applications, and abbreviated new drug applications.

(a) *New drug applications and biologics license applications.* The NDA or BLA applicant must submit to FDA for approval as part of the application the Patient Medication Information along with the PI upon which the Patient Medication Information is based. If Patient Medication Information is submitted after approval of the NDA or BLA, the Patient Medication Information, along with the PI upon which the Patient Medication Information is based, must be submitted to FDA for approval in a prior approval supplement pursuant to §§ 314.70(b)(2)(v)(B) and 601.12(f)(1) of this chapter.

(b) *Abbreviated new drug applications.* The abbreviated new drug application (ANDA) applicant must submit Patient Medication Information to FDA for approval after either Patient Medication Information for the reference listed drug is approved or FDA has finalized the Patient Medication Information template and provides notice of the template to the applicant, whichever applies. If Patient Medication Information is submitted after the original approval of the ANDA, Patient Medication Information must be submitted in a supplement to the ANDA consistent with § 314.70 of this chapter.

§ 208.70 Providing Patient Medication Information to patients.

(a) When a prescription drug product is used, dispensed, or administered to a patient (or the patient's agent) on an outpatient basis, the authorized dispenser of a prescription drug product for which Patient Medication Information is required under subparts A and B of this part must provide FDA-approved Patient Medication Information to each patient (or the patient's agent). Authorized dispensers may provide Patient Medication Information to the patient electronically; however, paper distribution must always be available.

(b) An authorized dispenser is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360) (which requires the registration of those that engage in the manufacture, preparation, propagation, compounding, or processing of drugs and the listing of certain drugs in commercial distribution) solely because of an action performed by the authorized dispenser under this part.

§ 208.80 Schedule for implementing the general requirements for Patient Medication Information.

(a) *Implementation schedule for applicants to submit Patient Medication Information for NDAs and BLAs.* NDA and BLA applicants must submit to FDA Patient Medication Information that conforms to the requirements in subparts A and B of this part. If an approved NDA or a BLA has one or more approved efficacy supplements, use the NDA, BLA, or efficacy supplement approval date that triggers the earliest submission for the following implementation schedule:

(1) For products for which an NDA, a BLA, or an efficacy supplement is submitted for approval on or after [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], a Patient Medication Information must be submitted to FDA as part of the application.

(2) For products for which an NDA, a BLA, or an efficacy supplement is pending on [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], a supplement or, if appropriate, an amendment, with Patient Medication Information must be submitted to FDA no later than 1 year after the date of approval of the pending application.

(3) For products with an FDA-approved Medication Guide (as required under subparts C and D of this part) or an FDA-approved patient package insert (as required under § 310.501 or § 310.515 of this chapter) for which an NDA or a BLA has been approved on or any time before [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], a supplement with Patient Medication Information must be submitted to FDA no later than [DATE 1 YEAR AFTER EFFECTIVE DATE OF FINAL RULE WILL BE ADDED]. Once the product with an FDA-approved Medication Guide (as required under subparts C and D of this part) or an FDA-approved patient package insert (as required under § 310.501 or § 310.515 of this chapter) has FDA-approved Patient Medication Information, the Medication Guide requirements (under subparts C and D of this part) and the patient package insert requirements (§§ 310.501 and 310.515 of this chapter) are no longer applicable to such product.

(4) For products without an FDA-approved Medication Guide or an FDA-approved patient package insert for which an NDA, a BLA, or an efficacy supplement has been approved any time from January 1, 2013, up to and including [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], a supplement with Patient Medication Information must be submitted to FDA no later than [DATE 2 YEARS AFTER EFFECTIVE

DATE OF FINAL RULE WILL BE ADDED].

(5) For products without an FDA-approved Medication Guide or an FDA-approved patient package insert for which an NDA, a BLA, or an efficacy supplement has been approved from January 1, 2008, up to and including December 31, 2012, a supplement with Patient Medication Information must be submitted to FDA no later than [DATE 3 YEARS AFTER EFFECTIVE DATE OF FINAL RULE WILL BE ADDED].

(6) For products without an FDA-approved Medication Guide or without an FDA-approved patient package insert for which an NDA, a BLA, or an efficacy supplement has been approved from January 1, 2003, up to and including December 31, 2007, a supplement with Patient Medication Information must be submitted to FDA no later than [DATE 4 YEARS AFTER EFFECTIVE DATE OF FINAL RULE WILL BE ADDED].

(7) For products without an FDA-approved Medication Guide or without an FDA-approved patient package insert for which an NDA, a BLA, or an efficacy supplement has been approved on or before December 31, 2002, a supplement with Patient Medication Information must be submitted to FDA no later than [DATE 5 YEARS AFTER EFFECTIVE DATE OF FINAL RULE WILL BE ADDED].

(b) *Implementation schedule for applicants to submit Patient Medication Information for ANDAs.* ANDA applicants must submit to FDA Patient Medication Information that conforms to the requirements in subparts A and B of this part and other applicable regulations.

(1) For products for which an ANDA is submitted for approval on or after [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], Patient Medication Information must be submitted to FDA as follows:

(i) If the Patient Medication Information for the reference listed drug is approved at the time the ANDA is submitted or if FDA has finalized the Patient Medication Information template and provides notice of the template to the applicant, whichever applies, Patient Medication Information must be submitted to FDA as part of the application.

(ii) If the Patient Medication Information for the reference listed drug is not approved or if FDA has not finalized the Patient Medication Information template and provided notice of the template to the applicant, whichever applies, at the time the ANDA is submitted but such Patient Medication Information is approved for the reference listed drug or FDA

finalizes the template and provides notice of the template to the applicant before the ANDA is approved, the applicant for the ANDA must submit Patient Medication Information in an amendment to the pending application after the approval of the Patient Medication Information for the reference listed drug or after FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant, whichever applies.

(iii) If the Patient Medication Information for the reference listed drug is not approved or if FDA has not finalized the Patient Medication Information template and provided notice of the template to the applicant, whichever applies, before the submitted ANDA is approved, a supplement with the Patient Medication Information must be submitted to FDA, consistent with § 314.70 of this chapter, after the approval of the Patient Medication Information for the reference listed drug or after FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant, whichever applies.

(2) For products for which an ANDA is pending on the [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], Patient Medication Information must be submitted as follows:

(i) If the Patient Medication Information for the reference listed drug is approved or if FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant before the ANDA is approved, an amendment to the pending application with Patient Medication Information must be submitted to FDA after the approval of the Patient Medication Information for the reference listed drug or after FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant, whichever applies.

(ii) If the Patient Medication Information for the reference listed drug is approved or if FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant after the pending ANDA is approved, a supplement with Patient Medication Information must be submitted to FDA, consistent with § 314.70 of this chapter, after the approval of the Patient Medication Information for the reference listed drug or after FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant, whichever applies.

(3) For products for which an ANDA has been approved on or any time before [EFFECTIVE DATE OF FINAL RULE WILL BE ADDED], a supplement with Patient Medication Information must be submitted to FDA, consistent with § 314.70 of this chapter, after the approval of the Patient Medication Information for the reference listed drug or after FDA finalizes the Patient Medication Information template and provides notice of the template to the applicant, whichever applies.

(c) *Implementation schedule for authorized dispensers to provide Patient Medication Information to patients.* Authorized dispensers must begin to provide FDA-approved Patient Medication Information as required under this section on [DATE 2 YEARS AFTER EFFECTIVE DATE OF FINAL RULE WILL BE ADDED] and must continue to provide FDA-approved Patient Medication Information thereafter. Once a product with an FDA-approved Medication Guide (as required under subparts C and D of this part) has FDA-approved Patient Medication Information, the requirements for providing a Medication Guide (under § 208.96) are no longer applicable for such product.

§ 208.90 Waivers.

On its own initiative or in response to a request from a covered entity, FDA may waive any Patient Medication Information requirement on the basis that the requirement is inapplicable, impracticable, or contrary to a patient's best interests (for example, impedes patient access to the drug product). FDA may consider an applicant's request for an extension from the specified implementation date to comply fully with the Patient Medication Information requirements. Written requests for waivers must be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product. For ANDAs, the requests for waivers and the rationale for the waiver would need to be submitted to the Director of the Office of Generic Drugs. For biological products, requests would be submitted to the FDA application division in the office with product responsibility.

Subpart C—General Provisions for Medication Guides for Prescription Drug Products

§ 208.91 Scope and purpose.

(a) Subparts C and D of this part set forth requirements for patient labeling for human prescription drug products, including biological products, that FDA determines pose a serious and

significant public health concern requiring distribution of FDA-approved patient information. It applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional. Subparts C and D of this part apply to new prescriptions and refill prescriptions.

(b) The purpose of patient labeling for human prescription drug products required under this part is to provide information when FDA determines in writing that it is necessary to patients' safe and effective use of drug products.

(c) Patient labeling will be required if FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect a patient's decision to use or to continue to use the product.

(3) The drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.

(d) Drug products described in § 208.10 must comply with subparts A and B of this part according to the implementation plan in § 208.80. Once a drug product has FDA-approved Patient Medication Information, the requirements for Medication Guides under subparts C and D of this part are no longer applicable.

§ 208.92 Definitions.

The following definitions apply to subparts C and D of this part:

Authorized dispenser means an individual who is licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide prescription drug products in the course of professional practice.

Dispensed means the act of providing a prescription drug product to a patient (or a patient's agent) by either of the following ways:

(1) By a licensed healthcare provider (or a licensed provider's agent), either directly or indirectly, for administration by the patient (or the patient's agent) or outside the licensed provider's direct supervision.

(2) By an authorized dispenser (or authorized dispenser's agent) under a lawful prescription of a licensed healthcare provider.

Distribute means the act of delivering, other than by dispensing, a drug product to any person.

Distributor means a person who distributes a drug product.

Drug product means a finished dosage form (for example, tablet, capsule, solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. For the purposes of this part, drug product also includes a biological product licensed under section 351(a) and (k) of the Public Health Service Act (42 U.S.C. 262(a) and (k)).

Licensed healthcare provider means an individual who is licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to prescribe drug products in the course of professional practice.

Manufacturer means all of the following:

(1) For a drug product that is not also a biological product, both the manufacturer as described in § 201.1 of this chapter and the applicant as described in § 314.3(b) of this chapter.

(2) For a drug product that is also a biological product, the manufacturer as described in § 600.3(t) of this chapter.

Medication Guide means FDA-approved patient labeling conforming to the specifications set forth in subparts C and D of this part and other applicable regulations.

Packer means a person who packages a drug product.

Patient means any individual to whom a drug product is intended to be, or has been, used, dispensed, or administered.

Serious risk or serious adverse effect means an adverse drug experience, or the risk of such an experience, as that term is defined in §§ 310.305, 312.32, 314.80, and 600.80 of this chapter.

Subpart D—General Requirements for Medication Guides for Prescription Drug Products

§ 208.94 Content and format of a Medication Guide.

(a) A Medication Guide must meet all of the following conditions:

(1) The Medication Guide must be written in English, in nontechnical, understandable language, and shall not be promotional in tone.

(2) The Medication Guide must be scientifically accurate and must be based on, and must not conflict with, the approved professional labeling for the drug product under § 201.57 of this chapter, but the language of the Medication Guide need not be identical to the sections of approved labeling to which it corresponds.

(3) The Medication Guide must be specific and comprehensive.

(4) The letter height or type size must be no smaller than 10 points (1 point =

0.0138 inches) for all sections of the Medication Guide, except the manufacturer's name and address and the revision date.

(5) The Medication Guide must be legible and clearly presented. Where appropriate, the Medication Guide must also use boxes, bold or underlined print, or other highlighting techniques to emphasize specific portions of the text.

(6) The words "Medication Guide" must appear prominently at the top of the first page of a Medication Guide. The verbatim statement "This Medication Guide has been approved by the U.S. Food and Drug Administration" must appear at the bottom of a Medication Guide.

(7) The brand name and established or proper name of the drug product must appear immediately below the words "Medication Guide." The established or proper name must be no less than one-half the height of the brand name.

(b) A Medication Guide must contain those of the following headings relevant to the drug product and to the need for the Medication Guide in the specified order. Each heading must contain the specific information as follows:

(1) The brand name (*e.g.*, the trademark or proprietary name), if any, and the established or proper name. Those products not having an established or proper name must be designated by their active ingredients. The Medication Guide must include the phonetic spelling of either the brand name or the established name, whichever is used throughout the Medication Guide.

(2) The heading "What is the most important information I should know about (*name of drug*)?" followed by a statement describing the particular serious and significant public health concern that has created the need for the Medication Guide. The statement must describe specifically what the patient should do or consider because of that concern, such as weighing particular risks against the benefits of the drug, avoiding particular behaviors (*e.g.*, activities, drugs), observing certain events (*e.g.*, symptoms, signs) that could prevent or mitigate a serious adverse effect, or engaging in particular behaviors (*e.g.*, adhering to the dosing regimen).

(3) The heading "What is (*name of drug*)?" followed by a section that identifies a drug product's indications for use. The Medication Guide must not identify an indication unless the indication is identified in the INDICATIONS AND USAGE section of the professional labeling for the product as required under § 201.57 of this chapter. In appropriate circumstances,

this section may also explain the nature of the disease or condition the drug product is intended to treat, as well as the benefit(s) of treating the condition.

(4) The heading "Who should not take (*name of drug*)?" followed by information on circumstances under which the drug product should not be used for its labeled indication (its contraindications). The Medication Guide must contain directions regarding what to do if any of the contraindications apply to a patient, such as contacting the licensed provider or discontinuing use of the drug product.

(5) The heading "How should I take (*name of drug*)?" followed by information on the proper use of the drug product, such as:

(i) A statement stressing the importance of adhering to the dosing instructions, if this is particularly important;

(ii) A statement describing any special instructions on how to administer the drug product, if they are important to the drug's safety or effectiveness;

(iii) A statement of what patients should do in case of overdose of the drug product; and

(iv) A statement of what patients should do if they miss taking a scheduled dose(s) of the drug product, where there are data to support the advice, and where the wrong behavior could cause harm or lack of effect.

(6) The heading "What should I avoid while taking (*name of drug*)?" followed by a statement or statements of specific, important precautions patients should take to ensure proper use of the drug, including:

(i) A statement that identifies activities (such as driving or sunbathing) and drugs, foods, or other substances (such as tobacco or alcohol) that patients should avoid when using the medication;

(ii) A statement of the risks to mothers and fetuses from use of the drug during pregnancy if specific, important risks are known;

(iii) A statement of the risks of the drug product to nursing infants if specific, important risks are known;

(iv) A statement about pediatric risks if the drug product has specific hazards associated with its use in pediatric patients;

(v) A statement about geriatric risks if the drug product has specific hazards associated with its use in geriatric patients; and

(vi) A statement of special precautions if any, that apply to the safe and effective use of the drug product in other identifiable patient populations.

(7) The heading “What are the possible or reasonably likely side effects of (*name of drug*)?” followed by:

(i) A statement of the adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently.

(ii) A statement of the risk, if there is one, of patients’ developing dependence on the drug product.

(iii) For drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act, the following verbatim statements: “Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.”

(8) General information about the safe and effective use of prescription drug products, including:

(i) The verbatim statement “Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide” followed by a statement that patients should ask health professionals about any concerns and a reference to the availability of professional labeling;

(ii) A statement that the drug product should not be used for a condition other than that for which it is prescribed or be given to other persons;

(iii) The name and place of business of the manufacturer, packer, or distributor of a drug product that is not also a biological product, or the name and place of business of the manufacturer or distributor of a drug product that is also a biological product, and in any case, the name and place of business of the dispenser of the product may also be included; and

(iv) The date, identified as such, of the most recent revision of the Medication Guide, placed immediately after the last section.

(9) Additional headings and subheadings may be interspersed throughout the Medication Guide, if appropriate.

§ 208.96 Distributing and providing a Medication Guide.

(a) The manufacturer of a drug product for which a Medication Guide is required under this part must obtain FDA approval of the Medication Guide before the Medication Guide may be distributed.

(b) Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients by either:

(1) Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to

provide a Medication Guide to each patient receiving a prescription for the drug product; or

(2) Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

(c) Each distributor or packer that receives Medication Guides or has the means to produce Medication Guides from a manufacturer under paragraph (b) of this section must provide those Medication Guides or the means to produce Medication Guides to each authorized dispenser to whom it ships a container of drug product.

(d) The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part must instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and must state how the Medication Guide is provided. These statements must appear on the label in a prominent and conspicuous manner.

(e) Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part must, when the product is dispensed, provide a Medication Guide directly to each patient (or to the patient’s agent) unless an exemption applies under § 208.98.

(f) An authorized dispenser or wholesaler is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution, solely because of an act performed by the authorized dispenser or wholesaler under this part.

§ 208.98 Exemptions and deferrals.

(a) FDA on its own initiative or in response to a written request from an applicant may exempt or defer any Medication Guide content or format requirement—except those requirements in § 208.94(a)(2) and (6)—on the basis that the requirement is inapplicable, unnecessary, or contrary to patients’ best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the FDA application division in the office with product responsibility.

(b) If the licensed provider who prescribes a drug product subject to this

part determines that it is not in a particular patient’s best interest to receive a Medication Guide because of significant concerns about the effect of a Medication Guide on the patient, the licensed provider may direct that the Medication Guide not be provided to the particular patient. However, the authorized dispenser of a prescription drug product subject to this part must provide a Medication Guide to any patient who requests information when the drug product is dispensed, regardless of any such direction by the licensed provider.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 6. The authority citation for part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 371, 374, 379e, 379k–1.

■ 7. In § 314.70, revise paragraph (b)(2)(v)(B) and add paragraph (c)(6)(iv) to read as follows:

§ 314.70 Supplements and other changes to an approved NDA.

* * * * *

(b) * * *

(2) * * *

(v) * * *

(B) If applicable, any change to Medication Guides required under part 208 of this chapter, except for changes in the information specified in §§ 208.40(a)(4), (7), and (8), and (c)(3) of this chapter, and § 208.94(b)(8)(iii) and (iv) of this chapter; and

* * * * *

(c) * * *

(6) * * *

(iv) Addition of Patient Medication Information for a drug approved under an ANDA if the proposed Patient Medication Information is the same as that approved for the reference listed drug or the same as the Patient Medication Information template finalized by FDA, whichever applies, except for permissible differences consistent with § 314.94(a)(8)(iv).

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

■ 8. The authority citation for 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.

■ 9. Add § 606.123 to subpart G to read as follows:

§ 606.123 Medication Guides: Patient Medication Information for blood and blood components intended for transfusion.

Medication Guides: Patient Medication Information (as described in part 208 of this chapter) must be provided to a patient who is administered blood or blood components on an outpatient basis unless a waiver is granted.

(a) Blood establishments must make Patient Medication Information (as described in part 208 of this chapter) available for distribution to the transfusion service. Licensed blood establishments must submit Patient Medication Information to FDA for approval (as described in part 208 of this chapter).

(b) When blood or blood components are administered on an outpatient basis,

the transfusion service must provide Patient Medication Information to each patient (or the patient's agent). The transfusion service may provide Patient Medication Information to the patient electronically; however, paper distribution must always be available.

(c) On its own initiative or in response to a written request from a blood collection establishment or transfusion service, FDA may waive any Patient Medication Information requirement on the basis that the requirement is inapplicable, unnecessary, impracticable, or contrary to a patient's best interests. Written requests for waivers must be submitted to the FDA application division in the office with product responsibility.

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

■ 10. The authority citation for 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.

§ 610.60 [Amended]

■ 11. Amend § 610.60 by removing paragraph (a)(7).

Dated: May 19, 2023.

Robert M. Califf,

Commissioner of Food and Drugs.

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