Supporting Statement
Reporting Requirements
PRESCRIPTION DRUG PRODUCT LABELING
MEDICATION GUIDE REQUIREMENTS
OMB Control No. 0910-0393

A. JUSTIFICATION

1. Circumstances of Information Collection

Food and Drug Administration (FDA) regulations require the distribution of patient labeling, called Medication Guides, for certain prescription human drug and biological products used primarily on an outpatient basis that pose a serious and significant public health concern requiring distribution of FDA-approved patient medication information. These Medication Guides inform patients about the most important information they should know about these products in order to use them safely and effectively. Included is information such as the drug's approved uses, contraindications, adverse drug reactions, and cautions for specific populations, with a focus on why the particular product requires a Medication Guide. These regulations are intended to improve the public health by providing information necessary for patients to use certain medication safely and effectively.

The regulations contain the following reporting requirements that are subject to the PRA. The estimates for the burden hours imposed by the following regulations are listed in the table 1 of this document:

21 CFR 208.20 – Applicants must submit draft Medication Guides for FDA approval according to the prescribed content and format.

21 CFR 314.70(b) (3) (ii) and 21 CFR 601.12(f) -- Application holders must submit changes to Medication Guides to FDA for prior approval as supplements to their applications,

21 CFR 208.24(e) -- Each authorized dispenser of a prescription drug product for which a Medication Guide is required, when dispensing the product to a patient or to a patient's agent, must provide a Medication Guide directly to each patient unless an exemption applies under 21 CFR 208.26.

21 CFR 208.26 (a) -- Requests may be submitted for exemption or deferral from particular Medication Guide content or format requirements.

2. Purpose and Use of Information

This information collection enables the agency to determine whether the labeling for certain prescription drug products that FDA has designated as posing a serious and significant public health concern requiring distribution of FDA-approved patient medication information include Medication Guides that are acceptable to FDA.

3. Use of Improved Information Technology

In the Federal Register of December 11, 2003 (68 FR 69009), FDA published a final rule amending its regulations governing the format in which certain labeling is required to be submitted for review with NDAs, certain biological license applications, ANDAs, supplements, and annual reports. The final rule requires that certain labeling content be submitted electronically in a form that FDA can process, review, and archive.

FDA has also issued the following guidance documents, among others, to explain the process for submitting information to the agency in electronic format:

- "Providing Regulatory Submissions in Electronic Format—NDAs." This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs. Among other things, the guidance provides recommendations on how to submit "labeling text" in electronic format. "Labeling text" is the term used in the guidance to mean labeling required under 21 CFR 201.100(d)(3), including all text, tables, and figures required by or included under those sections. The guidance recommends that labeling text be submitted as a PDF file.
- "Providing Regulatory Submissions in Electronic Format--General Considerations." This guidance includes a description of the types of electronic file formats that we are able to accept to process, review, and archive electronic regulatory submissions. The guidance also states that

documents submitted in electronic format should, among other things, enable you to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page, as it would have been provided in paper, while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents. To achieve these and other goals, the guidance recommends that all electronic regulatory submissions be submitted as PDF files.

- "Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format." This guidance provides information to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).

• "Providing Regulatory Submissions in Electronic Format —Prescription Drug Advertising and Promotional Labeling." This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

• "Providing Regulatory Submissions in Electronic Format—ANDAs." This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

• "Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs." This draft guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

• "Providing Regulatory Submissions in Electronic Format-—Postmarketing Periodic Adverse Drug Experience Reports." This guidance discusses general issues related to the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

• "Providing Regulatory Submissions in Electronic Format-—Human Pharmaceutical Product Applications and Related Submissions." This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional labeling.

• "Providing Regulatory Submissions in Electronic Format-—General

Considerations." This draft guidance discusses general issues common to all types of electronic regulatory submissions.

• "Providing Regulatory Submissions in Electronic Format-—Content of Labeling." This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

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

4. Efforts to Identify Duplication

The reporting required as a result of this information collection is not currently required by FDA and would not duplicate any other information collection.

5. Involvement of Small Entities

The reporting would apply equally to all applicants and dispensers whether large or small. However, because the number of products requiring Medication Guides overall will be relatively small, the smaller applicants would arguably sponsor many fewer drug products requiring Medication Guides and would, therefore, have fewer reporting responsibilities.

6. Consequences If Information Collected Less Frequently

The frequency of this reporting requirement would be determined by the applicant’s number of marketed prescription drug products that need a Medication Guide.

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

There is no inconsistency.

8. Consultations Outside the Agency

In the FEDERAL REGISTER of March 18, 2008 (73 FR 14471), FDA published an opportunity for public comment on this proposed collection of information. We received 4 comments.

1. The comments said that FDA's estimate of the hourly burden for pharmacists to comply with the Medication Guide requirements is inaccurate, and that pharmacists spend significantly more time determining whether a Medication Guide is required, tracking appropriate Medication Guides from manufacturers or distributors, explaining to the patient what the Medication Guide is, in addition to patient counseling. The comments noted that FDA's estimate that a pharmacist spends 0.0014 hours (5 seconds) to distribute each Medication Guide remains unchanged since the December 1, 1998, final rule entitled "Prescription Drug Product Labeling; Medication Guide Requirements," even though the Medication Guide program has continued to expand. The comments said that FDA's estimates are inadequate and fail to consider the operational realities pharmacists now face in complying with the program. The comments said that pharmacy personnel spend tens of thousands of hours obtaining and distributing Medication Guides for each new prescription and all refills for Medication Guide medications.

FDA Response: FDA agrees with the comments. However, the comments did not suggest an alternative burden estimate for Medication Guide distribution by pharmacists. We are increasing the burden estimate for § 208.24(e) to 3 minutes for each Medication Guide distributed by pharmacists. If the commenters believe that this estimate is insufficient, we request comments on why an alternative estimate would be more accurate. We are also increasing to 25 the number of Medication Guides that FDA receives per year under § 208.20.

2. The comments also said that there are distributor costs to comply with the Medication Guide requirements and Table 1 in the March 18, 2008, Federal Register notice omitted § 208.24(c), which provides that "Each distributor or packer that receives

Medication Guides…shall provide those Medication Guides…to each authorized dispenser to whom it ships a container of drug product." The comments said that the burden to distributors and packers to distribute Medication Guides -- the process of tracking, sorting, matching, and shipping multiple versions of Medication Guides for multiple products – should be included in the analysis.

FDA Response: FDA agrees with the comments and is willing to include a burden estimate for § 208.24(c). We are requesting comments on specific estimates for this requirement.

3. The remaining issues raised by the comments in response to the March 18, 2008, Federal Register notice are generally the same as the issues raised during FDA's public hearing on the use of Medication Guides to distribute drug risk information to patients (announced in the Federal Register of April 9, 2007 (72 FR 17559)) and the same as the comments submitted to that docket. (One commenter also referenced comments previously submitted to FDA in the "June 2006 White Paper on *Patient Safety Implications on Implementation of the Current FDA-Mandated Medication Guide Program*"). On July 2, 2007, FDA posted a "Summary of Public Hearing on FDA's Use of Medication Guides to Distribute Drug Risk Information to Patients" at http://www.fda.gov/cder/meeting/SummaryPublicHearingMedicationGuides.htm. The issues raised in conjunction with the public hearing, as well as the comments summarized below, are still under consideration at FDA and we have not yet decided what actions we will take in response to suggestions to modify the Medication Guide program.

The following is a summary of the comments received on the March 18, 2008, notice that do not pertain to the specific burden estimates.

4. The comments said that despite stating in the Medication Guide final rule that FDA will use Medication Guides sparingly, the agency continues to add new Medication Guides for drugs in a manner inconsistent with its original intent. The comments said that FDA intended Medication Guides to be used only when a drug posed very serious or significant side effects, and that it anticipated the program to be limited to a small number of products, and not more than 5 to 10 products per year. The comments said that by 2004, about 20

products required Medication Guides, and that starting in 2005, FDA began requiring Medication Guides for entire medication classes, which have grown to include antidepressants, non-steroidal anti-inflammatory drugs, and attention deficit hyperactivity disorder and sleep disorder drugs. The comments said that today almost 300 million prescriptions per year for over 10,000 separate drug products are subject to the Medication Guide requirement, and pharmacists are dispensing Medication Guides for substantially more drugs than originally estimated. The comments said that this has created significant burdens for pharmacists.

5. The comments said that there is no evidence that a Medication Guide is a good vehicle for risk communication, and FDA has not provided evidence that the program is valuable to patients or improves the safe and effective use of prescription drugs. The comments said that given the amount of information patients are likely to receive with their prescriptions, they face a tremendous challenge in actually reading each piece of information. As a result, the comments said, many patients are likely to not read any material provided to them. Those patients that desire to gain additional information about their therapy but are unable to read each document are placed in a position of having to decide which document distributed to them is more important than the other. The comments said that FDA should first evaluate whether patients actually read the Medication Guides distributed to them, and then assess whether the information contained in a Medication Guide is easily understood by patients. The comments said that many patients are likely to find the information difficult to understand or confusing, and that many patients, especially older and disabled patients, have cognitive impairments that may pose tremendous challenges in understanding information contained in a Medication Guide. The comments also asked whether the information contained in the Medication Guide is already available to patients. For example, the

comments said that pharmacists provide counseling on the safe and effective use of medication to their patients at the time of dispensing, and are able to translate highly complex information about a drug's characteristics, use parameters, side-effects and abuse potential. The comments said this counseling by pharmacists, coupled with other information already distributed to patients, such as consumer medication information and the patient package insert or the patient information sheet, raises questions about the need for the Medication Guide program. The comments also said that FDA has not made sufficient data available to the public to support the position that the Medication Guide program is important to communicate risk, and FDA should release all data from its surveys and studies for review and comment by health care provider groups. The comments said that this data will help generate a more accurate estimate of the burden imposed on the public as a result of the Medication Guide program.

6. The comments said that pharmacists face difficulties in obtaining Medication Guides. The comments said that some Medication Guides are included with the product itself in the package insert, some are provided in tear-off sheets, and some are available electronically. The comments said that the lack of a standardized delivery model complicates efforts to operationally streamline dispenser and distribution systems for duplicating and providing Medication Guides. In addition, pharmacists at times need to call a toll free number to order hard copies of the Medication Guides for distribution. The comments said that FDA should establish standards for manufacturer distribution of medication guides and establish a single toll free number or Internet site for pharmacies to use to obtain Medication Guides.

7. The comments said that FDA should waive certain Medication Guide formatting requirements to permit pharmacies to print Medication Guides through existing pharmacy computer systems. The comments said that permitting pharmacies to print Medication Guides would enhance their distribution and will free pharmacists' time to use

for patient counseling and care. The comments also said FDA should permit pharmacies to e-mail Medication Guides to their patients.

8. The comments said that a single, uniform Medication Guide should be used for all brand and generic versions of the same drug, or for drugs within the same therapeutic class, with similar risk warnings, and that each brand and generic manufacturer of the same drug or the same class of drug should not have to produce its own Medication Guide. The comments said that for medications that have unique and rare side effects that are not shared with the other drugs in the same class, FDA should consider having a class Medication Guide that specifically lists per paragraph each drug in the class while highlighting risk information that is unique to certain medications within that class.

9. The comments said that Medication Guides should only be required the first time a prescription is filled, and thereafter only when requested by a patient for that prescription's refill.

10. The comments said to eliminate duplication and enhance the usefulness of patient information, a single, manufacturer-produced, patient-oriented FDA-approved Medication Information Document should be developed for each drug that currently requires a Medication Guide. This single document could combine consumer mediation information and Medication Guide information. The comments said they are willing to work with FDA and other interested stakeholders in designing and implementing such a program. Alternatively, the comments said that FDA should standardize the information that must be included in the Medication Guide and require a consistent format, look, and feel to Medication Guide information.

11. The comments said that physicians and other providers should give the Medication Guide directly to the patient at the time the prescription is written. The comments said the physician is in the best position to discuss not only the possible risks associated with the medication but to also discuss alternative therapies if necessary. The comments also said that FDA should consider ways that prescribers could be better informed about medications that require Medication Guides.

12. The comments said that the Medication Guide requirements were imposed on distribution and dispensing entities that were neither prepared nor operationally structured (for example, lack of space, staff, and equipment) to prepare and provide for their dissemination.

9. Remuneration of Respondents

There is no payment to respondents

10. Assurance of Confidentiality

This reporting burden has no confidentiality implications.

11. Question of a Sensitive Nature

This reporting burden does not involve any sensitive question.

12. Estimates of Annualized Hour Burden

Estimated Annual Reporting Burden

Table 1 - Estimated Annual Reporting Burden

21 CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours Per Response	Total Hours
208.20	25	1	25	320	8,000
314.70 (b)(3)(ii) 601.12(f)	5	1	5	72	360
208.24(c)	191	9,000	1,719,000	1.25	2, 148, 750
208.24(e)	59,000	5,000	295 million	3 minutes	14,750,000
208.26(a)	1	1	1	4	4
Total					16,907,114

13. Estimates of Annualized Cost to Respondents

FDA estimates that, on average, approximately 25 Medication Guides would be submitted annually. If each Medication Guide requires approximately 320 hours to prepare and submit to FDA, the industry cost, based on and hourly rate of $60 per hour, would be approximately $480,000. FDA also estimates that the cost of developing each Medication Guide to supplement existing applications would be approximately $5000, and the cost for each generic drug Medication Guide would be approximately $500.

FDA estimates that the sponsor of one of the new or supplementary applications will request an exemption under § 208.26(a) from at least some of the Medication Guide format or content requirements. FDA estimates that this will entail approximately 4 hours of work, or approximately $240.

In addition, FDA estimates that 5 existing Medication Guides annually might require minor change under § 314.70 (b)(3)(ii) or § 601.12 (f), necessitating 360 hours of full-time effort.

Under § 201.24(e), authorized dispensers are required to provide a Medication Guide directly to the patient (or the patient's agent) upon dispensing a product for which a Medication Guide is required. Based on comments we received (see section 8, comment 1), FDA has increased the burden estimate for § 208.24(e) from approximately 5 seconds (.0014 hour) to 3 minutes for a pharmacist to distribute a Medication Guide to a patient.

14. Estimates of Annualized Cost Burden to the Government

FDA and industry sponsors currently work to ensure the development and distribution of patient labeling on a product-by-product basis, and FDA reviews all labeling submitted under an NDA. This requirement provides greater clarity about what products will require Medication Guides and what the format and content requirements will be. Thus, there should be no additional costs to the Federal Government, and no additional FTE's will be needed.

15 Change in Burden

The change in burden is the result of new data on the number of submissions.

16 Time Schedule, Publication, and Analysis Plans

FDA does not intend to publish tabulated results of the information collection requirements that would be imposed by these requirements.

17. Displaying of OMB Approval Date

There are no forms associated with this collection of information.

18. Exception to the Certification Statement – Item 19

There are no exceptions to the certification statement "Certification for Paperwork Reduction Act Submission."