

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 208, and 209

[Docket No. FDA-2003-N-0313] (formerly Docket No. 2003N-0342)

RIN 0910-AC35

**Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule that confirms the interim final rule entitled “Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products” (73 FR 402, January 3, 2008) (interim final rule) and responds to comments submitted in response to the request for comments in the proposed rule of the same title (69 FR 21778, April 22, 2004) (proposed rule). This final rule affirms the interim final rule’s requirement for the addition of a statement to the labeling for certain human drug products for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the act). The statement includes a toll-free number and advises that the number is to be used only for reporting side effects and is not intended for medical advice (the side effects statement). This final rule also affirms the interim final rule’s addition of new part 209 to the regulations requiring distribution of the side effects statement. This final rule implements provisions of the Best Pharmaceuticals for Children Act (the

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BPCA) and the Food and Drug Administration Amendments Act of 2007 (FDAAA).

**DATES:** *Effective Date:* This final rule is effective [*insert date 30 days after date of publication in the Federal Register*].

*Compliance Date:* The compliance date for this final rule is July 1, 2009. For more information on the compliance date see section II of the **SUPPLEMENTARY INFORMATION** section of this document.

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**SUPPLEMENTARY INFORMATION:**

**I. Background**

*A. BPCA and Proposed Rule*

The BPCA (Public Law 107-109) directed FDA to issue a final rule requiring the labeling of each human drug product for which an application is approved under section 505 of the act (21 U.S.C. 355) to include: (1) A toll-free number maintained by FDA for the purpose of receiving reports of adverse events regarding drugs and (2) a statement that the number is to be used for reporting purposes only, not to receive medical advice. Collectively, we refer to the toll-free number and reporting statement as the “side effects statement.” The BPCA stated that the final rule must implement the labeling requirement to reach the broadest consumer audience and minimize the cost to the pharmacy profession.

On April 22, 2004 (69 FR 21778), FDA published a proposed rule entitled “Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products.” FDA received 22 comments on the proposed rule. -

*B. FDAAA Requirements and Interim Final Rule*

On September 27, 2007, the President signed into law FDAAA (Public Law 110–85). Among other things, FDAAA reauthorized the BPCA. Section 502(f) of FDAAA stated that “the proposed rule \* \* \* ‘Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products’ \* \* \* shall take effect on January 1, 2008,” unless FDA issues a final rule before that date. FDA was in the process of analyzing the comments on the proposed rule and conducting research on consumer comprehension of the proposed side effects statements when FDAAA was enacted. FDA did not issue a final rule prior to January 1, 2008. Therefore, by operation of law, the proposed rule took effect on January 1, 2008.

FDAAA mandated one change to the proposed rule. Section 502(f)(2) of FDAAA states that the proposed rule shall not apply to over-the-counter (OTC) drugs marketed with an application approved under section 505 of the act (application OTC drug products) if these application OTC drug products meet certain labeling requirements.

On January 3, 2008 (73 FR 402), FDA published an interim final rule to: (1) Codify the modifications made by FDAAA to the proposed rule, (2) notify the public that the agency planned to complete the ongoing research testing the proposed side effects statements for consumer comprehension, and (3) establish a compliance date of January 1, 2009. The interim final rule stated that the agency did not intend to take enforcement action prior to January 1, 2009, and that the agency would complete the research on the side effects

statements and either finalize the interim final rule as published or publish a final rule that amends the interim final rule.

## **II. Highlights of the Final Rule**

The preamble to the proposed rule described the provisions of this rule in detail. In the preamble to the interim final rule we described the changes to the proposed rule required by FDAAA. In this final rule we respond to comments received on the proposed rule and finalize the regulations. No comments were received on the interim final rule.

As described in the interim final rule, one substantive change has been made to the regulatory provisions published in the proposed rule: Section 201.66(c)(5)(vii) (21 CFR 201.66(c)(5)(vii)) has been modified to require that only approved application OTC drug products whose packaging does not include a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug product are required to include the side effects statement in labeling. As discussed previously in this document, this modification was mandated by FDAAA.

In the interim final rule, FDA established a compliance date of January 1, 2009, and notified the public that we intended to exercise enforcement discretion and not take enforcement actions with regard to the effective regulations until January 1, 2009. In the interim final rule we stated that the effective date and implementation schedule for the final rule would be designed to minimize the burden of any additional regulatory changes for affected entities who must comply with the final rule. Since the publication of the interim final rule, we have received several inquiries about specific provisions of the interim final rule. Given the short time interval between the publication date of this final rule and the original compliance date of January

1, 2009, we are delaying the compliance date by six months to July 1, 2009. We believe this brief delay is appropriate because we have made no changes to the codified. All affected entities are required to be in compliance by July 1, 2009.

### **III. Comments and Agency Response**

The agency received 22 comments on the proposed rule. Comments were received from prescription and nonprescription drug manufacturers; trade organizations representing drug manufacturers; pharmacists, pharmacies, and pharmacy-related interests; consumer organizations; professional associations and organizations; one member of Congress; one agency of a foreign government; and others.

To make it easier to identify comments and our responses, the word “Comment,” in parentheses, appears before the comment’s description, and the word “Response,” in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value or importance or the order in which it was received. A summary of the comments received and our responses follow.

#### *A. Scope of the Rule*

(Comment 1) The agency received 7 comments opposing the proposed requirement that the labeling for application OTC drug products contain the toll-free number and statement mandated by the BPCA. These comments argued that Congress did not intend the BPCA requirements to apply to application OTC drug products.

(Comment 2) Two comments suggested that FDA limit the applicability of the regulatory provisions to new drugs that have been approved for marketing within 5 years of the date of the final rule, and that the regulation's requirements attach for only 5 years following a new drug's approval. These comments requested that FDA limit the regulatory provisions to the approximately 30 new molecular entities (NMEs) that are approved each year for the 5-year period after they are approved and suggested that reporting should be targeted to encourage consumer reporting of adverse reactions from newer drugs.

(Response) Section 17 of the BPCA required that the labeling of each drug for which an application is approved under section 505 of the act include the toll-free number and statement. Because OTC drug products may be approved under section 505 of the act, we proposed that the labeling for all application OTC drug products contain the BPCA mandated requirements. However, in section 502(f)(2) of FDAAA, Congress stated that the proposed rule shall not apply to OTC drugs marketed with an application approved under section 505 of the act if these application OTC drug products meet certain labeling requirements. Specifically, section 505(f)(2) of the act states that the proposed rule shall not apply to a drug: (1) For which an application is approved under section 505 of the act; (2) that is not described under section 503(b)(1) of the act (21 U.S.C. 353(b)(1)); and (3) the packaging of which includes a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug. In the interim final rule, we stated that this provision means that the proposed provisions do not apply to application OTC drug products if the product's packaging includes a manufacturer's or distributor's toll-free number for reporting complaints. Accordingly, this final rule includes

a modified § 201.66(c)(5)(vii) reflecting the changes to the proposed rule required by FDAAA.

As to the comments suggesting that we limit the scope of the rule to a specific subset of NMEs or for a specific number of years for specific products, we note that neither the BPCA nor FDAAA gives FDA the legal authority to limit the scope of the rule in this way. The BPCA requires that the labeling of each drug product approved under section 505 of the act, regardless of the date on which approved, include the side effects statement.

*B. Wording of the Side Effects Statement*

As stated in the preamble to the proposed rule, section 17 of the BPCA requires that the labeling for each drug approved under section 505 of the act include: (1) A toll-free number maintained by FDA for the purpose of receiving reports of adverse events regarding drug products and (2) a statement that the number is to be used for reporting purposes only, not to seek medical advice. FDA considered these requirements and proposed a conforming statement for prescription drug products: “Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.”

As stated in the preamble to the proposed rule, the drug facts labeling format for OTC drug products required us to modify the side effects statement to correspond to the drug facts format (§ 201.66). The OTC requirement was included in the specific subheadings for presenting warnings in the drug facts format (§ 201.66(c)(5)(vii)). In combination with the requirements of § 201.66(c)(5)(vii), the labeling provision for the application OTC drug products was proposed to read: “Stop use and ask a doctor if • side effects occur. You may report side effects to FDA at 1–800–FDA–1088.”

We solicited comments on the proposed wording of the side effects statements and on whether the term “side effects” should be further qualified.

(Comment 3) We received several comments suggesting that we test on consumers the proposed language for the side effects statements, as well as alternatives, to evaluate consumer comprehension and determine the best and most precise terminology for the statement.

(Comment 4) Among the comments we received on the proposed wording of the side effects statement, one comment asserted that the proposed statement is concise and makes it clear that the number is not for medical advice. Several comments suggested specific additions to the wording of the statements, including: Using the term “health care professional” instead of, or in addition to, the term “doctor”; adding the term “pharmacist” to the statement to suggest that consumers call either their doctor or pharmacist for medical advice about side effects; adding wording to clarify that FDA does not give medical advice and is not offering medical consultation; and/or adding wording to clarify that FDA should not be called in case of medical emergency and that FDA should only be called once any medical emergency is resolved.

(Comment 5) Of the six comments we received on whether to use the term “side effects” or “adverse event,” five supported use of the term “side effects” as more consumer friendly. Of those comments, two suggested qualifying the term with “serious” and one opposed adding any qualifications to the term. Those suggesting qualifying the term were concerned about FDA receiving numerous unnecessary reports about side effects that are well-known and expected, not serious; the comment opposed to qualifying the term was concerned that qualifying the statement would limit the types of events reported, discourage consumers from reporting, and hinder the agency’s ability

to identify trends from reporting. One comment suggested that use of the term “side effects” would have a negative effect on drug marketing.

(Comment 6) Among the comments we received on the wording of the side effects statement for application OTC drug products were comments opposing the inclusion of the statement in the “warnings” section of the drug facts format and the specific “stop use” language that section requires. One comment suggested placing the side effects statement under the “when using this product” subheading as the last bullet, so that the labeled adverse events precede the side effects statement. Comments opposed the “stop use” language on the grounds that stopping use of an OTC drug product may be inappropriate. Comments also stated that the “stop use” language has a greater impact on OTC drug products than it does on prescription drug products, i.e., there is no corresponding requirement telling consumers using prescription drug products to stop using the product if they experience a side effect. Several comments also stated that because the drug facts format requires a telephone number for consumers to call to get answers to questions, there would be confusion caused by having more than one phone number in the labeling for consumers to call.

(Response) After reviewing the comments received on the proposed rule, FDA initiated a two-part study to test consumer comprehension of the wording of the proposed side effects statements. Part one of the study consisted of focus groups held to narrow the field of potential statement alternatives. When describing the side effects statement for prescription drug products, participants in the focus groups were asked whether they preferred the use of “doctor” or “health care provider,” “doctor” or “doctor or pharmacist,” “serious side effects” or “side effects,” and “adverse events” or “side effects,”

in the statement, as well as other language variations. The focus groups were completed in 2006 (OMB Control No. 0910–0497).

The second part of this research was a labeling comprehension experimental study conducted over the Internet (OMB Control No. 0910–0603). Nine statements were tested as informed by the prior focus group testing. A total of 1,674 men and women ranging in age from 21 to 95 with varying levels of education completed the study. Five different versions of the side effects statement for prescription drug products and four different versions of the side effects statement proposed for application OTC drug products were tested. Approximately 40 percent of the sample of consumers saw one of the four OTC side effects statements and the other 60 percent of the sample saw one of the five prescription drug side effects statements. FDA's final report on the study was completed in 2008 and is available in the docket for this rule.

In answer to questions about the best wording for the side effects statement, only one of the statements tested was significantly less clear than the others. We eliminated this statement from consideration. All other statements were rated very similarly by participants. Participants who responded to the side effects statements for prescription drugs responded nearly identically to participants who responded to the side effects statements for OTC drug products. Given these results, FDA concluded that in choosing among the statements, considerations such as length, readability, and other factors could be used to select among the remaining side effects statements. Taking into account the results from the labeling comprehension study and other factors, we have chosen to finalize the side effects statements as originally proposed.

Additionally, to address comments received indicating concern that consumers would call FDA for medical advice and suggested language changes to prevent this, we queried participants in the study about whether they would choose to call FDA or their doctor in certain circumstances. Participants did not show an inclination to call FDA for medical advice. Among those that indicated a willingness to call FDA at all, the majority appropriately indicated that FDA was for reporting side effects and their doctors were for personal medical advice. Most individuals indicated that they would contact their doctor first regardless of the particular side effect they experienced. We conclude from this finding that the language proposed for the side effects statement is sufficient to convey the intention of the BPCA requirement that the statement is to be used for reporting purposes only, not to receive medical advice.

Similarly, with regard to concerns that we should qualify the type of side effect that should be reported to FDA by adding the word “serious” to “side effect” because FDA would receive numerous unnecessary reports, our research indicates that consumers are able to distinguish between serious and non-serious side effects and would contact their doctor or hospital emergency room in the case of a “serious side effect.” A doctor who determines that a patient has had a serious side effect from a drug product may then report the side effect to FDA.

Regarding the comments we received on the specific language of the OTC side effects statement and its placement in the “warnings” section of the drug facts format, we disagree that placement in the “warnings” section is inappropriate or that the “stop use” language is inappropriate. The warnings section of the drug facts format label for OTC drug products may include

several statements about possible side effects, telling consumers when to consult a doctor, pharmacist, or other health care professional in the use of the product. Consumers using OTC drug products most likely are not under the direct care of a health care practitioner, whereas consumers using prescription drug products are under the care of a health care practitioner. We believe it is appropriate for the side effects statement to instruct consumers using an OTC drug product who believe they are experiencing a side effect to stop using the drug product and consult their doctor before continuing use of the product.

We do not agree that having more than one phone number in the drug facts format labeling would be confusing to consumers. The agency's toll-free number clearly indicates it is an FDA phone number for reporting side effects. Our research indicates that the OTC side effects statement is understood by consumers. Moreover, section 502(f)(2) of FDAAA states that application OTC drug products that include a toll-free number through which consumers can report complaints to the manufacturer or distributor of the drug product are not required to include the side effects statement. In all likelihood this means that fewer application OTC drug products will have FDA's side effects statement in their labeling. Therefore, we anticipate that the majority of application OTC drug products will not have more than one phone number in their labeling for reporting side effects, reducing any potential for confusion.

### *C. Location of the Side Effects Statement in FDA-Approved Labeling*

We proposed to require the side effects statement in two categories of drug product labeling: (1) FDA-approved Medication Guides for drugs approved under section 505 of the act, and (2) the labeling for application OTC drug products. We stated that manufacturers voluntarily may include the side effects

statement in Medication Guides for products not approved under section 505 of the act or in patient package inserts (PPIs). For reasons stated in the proposed rule, we did not propose requiring the side effects statement in physician labeling or PPIs, but we solicited comments on those two issues. In addition, we proposed that the side effects statement be distributed with each prescription drug product, both new and refills, approved under section 505 of the act and dispensed to consumers by pharmacies and authorized dispensers in an outpatient setting.

(Comment 7) We received one comment stating that the side effects statement should be on all package labeling, including refills, to ensure maximum consumer exposure so that when consumers experience a side effect, they will find the side effects statement wherever they turn first for information.

(Comment 8) One comment suggested that instead of putting the side effects statement in drug product labeling, FDA's MedWatch telephone number appear in public telephone books next to the Poison Control phone number.

(Comment 9) Another comment suggested that consumers be given small magnets with FDA's MedWatch phone number obviating the need for repeated dispensing of this information each time a patient visits a pharmacy.

(Response) We believe that the requirements of this final rule will ensure that the side effects statement reaches a broad consumer audience while minimizing the burden on the pharmacy profession, as required by the BPCA. We require that the side effects statement appear in Medication Guides for drug products approved under section 505 of the act and in the labeling for certain application OTC drug products, and that pharmacies distribute the statement with all new prescriptions and refills for drug products approved under section

505 of the act. Under the BPCA, Congress required that FDA include the side effects statement in the labeling of each drug product approved under section 505 of the act. Placing the number in public telephone books or on magnets given to consumers would not satisfy the legal requirements of the BPCA.

(Comment 10) We received three comments supporting the inclusion of the side effects statement in approved Medication Guides. One comment suggested that this be the exclusive place for the labeling requirement. We do not agree that requiring the side effects statement exclusively in Medication Guides would satisfy the requirements of the BPCA. FDA-approved Medication Guides are prepared by manufacturers for a limited number of drug products that FDA determines pose a “serious and significant public health concern” (21 CFR 208.1). Given the limited number of drug products that have FDA-approved Medication Guides, only requiring the side effects statement in Medication Guides would not satisfy the BPCA requirement to reach the broadest consumer audience.

(Response) We did not propose including the side effects statement in physician labeling. In the proposed rule we stated that while consumers have access to physician labeling reprinted in the Physician Desk Reference (PDR), physician labeling is not written for the consumer audience. We solicited comments on this issue.

(Comment 11) We received one comment supporting our decision not to include the side effects statement in physician labeling. This comment agreed that physician labeling is not intended or written for a consumer audience and that it is not necessary to include both a manufacturer’s name and telephone number and FDA’s telephone number in physician labeling.

(Comment 12) We received three comments suggesting we require the side effect statement in physician labeling. These comments argued that some consumers may obtain physician labeling either over the Internet or upon request from their pharmacist and that FDA's toll-free number should be in all FDA-approved prescription labeling to ensure its widest exposure.

(Response) At the time the proposed rule was written, the agency's proposed rule to revise the physician labeling requirements in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57) was under review (the physician labeling rule). On January 24, 2006, the agency published the final physician labeling rule (71 FR 3922). Section 201.57 of the physician labeling rule requires that the following verbatim statement appear in the highlights section of the prescribing information under "adverse reactions" (§ 201.57(a)(11)(ii)): "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions)." As physician labeling is written for the medical profession, the term "adverse reactions" was selected for this statement instead of the more consumer-friendly term "side effects." While placing this newly required statement in the highlights section of physician labeling will alert consumers who consult or refer to physician labeling that they can report adverse reactions directly to FDA at the MedWatch telephone number or Web site, the agency concludes that pharmacies' distribution of only the physician labeling containing this statement would not be sufficient to satisfy the requirement of the BPCA to reach the broadest consumer audience. In addition, the statement required under the physician labeling rule does not include the statement required by the BPCA that the phone number be used only for

reporting side effects and not to obtain medical advice. Therefore, while the MedWatch phone number for reporting side effects has been added to physician labeling through the physician labeling rule, distributing physician labeling has not been added to this rule as a means for pharmacies to meet the requirements of distributing the side effects statement.

The proposed rule did not include the side effects statement in PPIs. PPIs are required by FDA for certain drug products, including oral contraceptives and estrogen drug products (21 CFR 310.501 and 310.515) and, in addition, some manufacturers also voluntarily produce PPIs for drug products. PPIs are based on physician labeling and are often distributed to consumers when the drug product is dispensed. In the preamble to the proposed rule, we stated that manufacturers may voluntarily include the side effects statement in PPIs. We solicited comments on this issue.

(Comment 13) We received five comments suggesting that we reconsider our decision not to include the side effects statement in PPIs. Of these four comments, one suggested that the PPI could be the first source of information consumers turn to when they experience a side effect; one suggested that it may be beneficial for consumers to see the statement more than once; one stated that including the statement in PPIs was a viable option; and two stated that requiring the side effects statement in PPIs would be a way to minimize the impact of the rule on pharmacies.

(Response) We have considered these comments and have concluded that, in consideration of the other requirements in this rule, requiring manufacturers to include the side effects statement in PPIs would have a minimal impact on meeting the goals of the BPCA. Furthermore, since drug products with FDA-approved PPIs are a subset of all prescription drug products, requiring the side

effects statement in PPIs would most likely require pharmacies to maintain a tracking system to identify which drug products have a compliant PPI in order for pharmacies to know whether they had distributed the side effects statement through the PPI in compliance with this rule. Therefore we conclude that it is unlikely that adding the statement to PPIs would minimize the burden of this rule on pharmacies, and it is more likely that pharmacies would choose one of the other proposed five methods of distributing the side effects statement. As stated in the preamble to the proposed rule, manufacturers may voluntarily add the side effects statement to PPIs, however we are not adding the distribution of a PPI to the list of options available to authorized dispensers or pharmacies for compliance with this rule.

(Comment 14) We did not require manufacturers to provide the side effects statement on labeling for unit-of-use drug products. We received three comments stating that FDA could minimize the impact of the rule on pharmacies by requiring manufacturers of unit-of-use drug products to provide the side effects statement on the labeling of the exterior package.

(Response) We have considered these comments and have concluded that the proposed provisions are adequate to address the goals of the BPCA to reach a broad consumer audience; therefore we are not requiring that manufacturers add the side effects statement to unit-of-use labeling. In addition, requiring the side effects statement in the labeling for unit-of-use drug products is unlikely to decrease the burden of this rule on pharmacies, since pharmacies would most likely have to maintain a tracking system to know whether they had distributed the side effects statement through dispensing a unit-of-use drug product in compliance with this rule. We believe it is more likely that pharmacies would choose one of the other five proposed methods of

distributing the side effects statement. Consumers will receive the side effects statement when the unit-of-use drug product is dispensed by an authorized dispenser or pharmacy using one of the five distribution methods proposed.

(Comment 15) We did not require health care practitioners who dispense drug samples in the course of their professional practice to distribute the side effects statement. The proposed rule stated that patients receiving drug products in these circumstances will rely on their health care practitioners to monitor and report adverse events. We received two comments asking us to require distribution of the side effects statement with drug samples.

(Response) Drug samples generally are given to consumers in conjunction with a new prescription. Patients who initially receive drug samples are under the care of their doctor or health care practitioner and generally use them in the short term and followup by filling a new prescription. For a drug product approved under section 505 of the act, consumers will receive the side effects statement upon filling the new prescription for the drug product for which they initially received a sample. We recognize that there may be situations in which health care practitioners provide drug samples to patients on an ongoing basis, such as in clinics for low-income patients. However such patients should be instructed by the health care practitioner providing the drug sample as to its directions for use and possible side effects. We do not believe that the benefit of requiring that the side effects statement be distributed with drug samples would be balanced by the burden such a requirement would impose on health care practitioners.

*D. Distribution of Side Effects Statement by Pharmacies and Authorized Dispensers*

We proposed that the side effects statement be distributed with each prescription drug product, both new and refills, approved under section 505 of the act and dispensed to consumers by pharmacies and authorized dispensers in an outpatient setting. We proposed five options through which pharmacies and authorized dispensers could distribute the side effects statement, including the following: (1) On a sticker attached to the package, vial, or container of the drug product; (2) on a preprinted pharmacy prescription vial cap; (3) on a separate sheet of paper; (4) in consumer medication information (CMI); or (5) by distributing the appropriate FDA-approved Medication Guide that contains the side effects statement. We solicited comments on other options pharmacies might use for distribution.

(Comment 16) We received one comment opposing a requirement to place the side effects statement directly on the label of the prescription vial or container. This comment stated that in many cases the vials or containers are already too crowded, and requiring another sticker on the container could crowd out more important labels and reduce the importance consumers ascribe to these labels both because of the number of stickers and because of the placement of secondary information in the stickers. We received one comment supporting the placement of the side effects statement on an auxiliary label. We received another comment stating that the most logical place for the side effects statement to appear is in the CMI for the drug product. Another comment suggested that CMI not be the only means of communicating the toll-free number, as some pharmacies may not dispense CMI for refill prescriptions.

(Comment 17) We received several comments supporting our proposal to provide multiple options for pharmacies and authorized dispensers to distribute the side effects statement. We received two comments stating that while we indicated we exercised discretion in giving affected pharmacies flexibility in complying with the law by providing options, we failed to impose a proportionate burden on manufacturers. One comment stated that it is entirely feasible for manufacturers to adhere multiple copies of printed leaflets onto bulk containers of drug products that pharmacy personnel can then remove from bulk containers and dispense with each prescription filled.

(Comment 18) We received two comments expressing concern about the potential for consumers to lose or dispose of paper messages (e.g., the consumer medication information option or the separate sheet of paper option). One of these comments requested that we require manufacturers and pharmacists to work together to include the side effects statement on either the sticker or preprinted vial cap with any separate printed materials provided as a supplement. This comment stated that if the package has no cap, if there is no room on a package for a sticker, or if the product already requires a sticker for a different reason, they would suggest that the sticker be included inside the package so that consumers can affix the sticker in a place useful to them, such as a medicine chest or pill caddy. Another comment requested that we allow pharmacies the option to distribute the side effects statement by printing it directly on the bag in which the pharmacy puts prescription drugs before handing them to consumers.

(Comment 19) Two comments requested that pharmacies be allowed the option to e-mail the side effects statement to consumers along with notice to these consumers that their prescriptions are ready. These comments stated that

this would obviate the need for the pharmacy to provide the patient with a paper version of the statement when the prescription is picked up. We received two comments requesting that we allow pharmacists to exercise their judgment and discretion in distributing the statement to a consumer if a pharmacist is reasonably sure that a consumer already knows about the agency's toll-free number.

(Response) We have considered the comments received and conclude that the range of options provided to pharmacies to distribute the side effects statement is adequate to meet the requirements of the BPCA. We disagree that placing the side effects statement on the pharmacy bag, sending the side effects statement by e-mail when a consumer is notified their prescription is ready, or providing the side effects statement on a separate sticker that consumers could then affix to their medicine chest or pill caddy would effectively reach the broadest consumer audience. While we recognize that a consumer may throw away any attachment a pharmacist provides when dispensing a drug product, including the CMI or a separate sheet of paper, there is an even greater likelihood that a consumer would throw away the pharmacy bag that the prescription came in or a small separate sticker, and thus would not have the side effects statement in proximity to the drug product when needed. Similarly, e-mail is easily deleted, and including the side effects statement in an e-mail notifying consumers when their prescription is ready makes it likely that the consumers will delete the e-mail before they even pick up the prescription.

Pharmacies may provide voluntarily a separate sticker to consumers with the side effects statement for attachment in the home as a public service if they choose; however, distribution of such a separate sticker would not meet

the distribution requirements of this rule. Similarly, pharmacies may provide the side effects statement voluntarily on pharmacy bags or via e-mail, but distribution of the side effects statement using these methods likewise would not meet the distribution requirements of this rule. Also, we note that there is no provision in the BPCA or FDAAA that would allow us to grant pharmacists the right to exercise their judgment or discretion in deciding whether or not to distribute the side effects statement to an individual consumer.

#### *E. Use of MedWatch System for Consumer Reporting*

As stated in the preamble to the proposed rule, we proposed that FDA's existing MedWatch system be used to fulfill the requirements of the BPCA for providing a toll-free number for the purpose of receiving adverse event reports regarding drug products. While we received comments supporting the use of the MedWatch system to capture consumer's postmarket safety information, we received several comments suggesting changes to the MedWatch system. These comments are beyond the scope of this rule. This rule does not make specific changes to the MedWatch system.

#### *F. Postmarketing Safety Reporting*

While the proposed rule suggested no changes to FDA's postmarketing safety reporting system, we received several comments about our postmarketing safety reporting system and how data received from the side effects statement would affect the system. These comments are beyond the scope of this rule. This rule does not make specific changes to FDA's postmarketing safety reporting system.

*G. Implementation of Regulation*

(Comment 20) We received one comment expressing dissatisfaction with the agency for not implementing the rule in a timelier manner. This comment also stated that the compliance date FDA proposed was too long and suggested a bifurcated compliance structure whereby pharmacies would notify consumers immediately of the toll-free number, and manufacturers would have 1 year to make any required labeling changes. We also received comments supporting the 1-year compliance period from both pharmacy interests and drug manufacturing interests. These comments noted that pharmacies and drug manufacturers need time to integrate any printing/labeling changes into existing systems.

(Response) In implementing the requirements of the BPCA and FDAAA, we believe it is important to work with stakeholders and provide time for updating labels and systems so that we reach the best possible outcome for constituent groups, including consumers, pharmacists and other health care professionals, drug manufacturers, and the agency. With the publication of this final rule, we believe we have implemented the provisions of the BPCA and FDAAA effectively.

(Comment 21) Two comments suggested that, after full implementation of the laws and all necessary modifications to the MedWatch system, FDA undertake extensive consumer outreach, educating the public about the right to report under the new provisions. One comment suggested that FDA, in cooperation with the OTC drug manufacturers, implement a public relations program to raise consumer awareness of the necessity of reporting unexpected adverse events to the product manufacturer. These comments stated that FDA should work with consumer educators and health professionals to provide

clear information and educational materials on how, what, and when to report. Another comment suggested the agency add specific questions to the ongoing National Survey of Prescription Medicine Information Received by Consumers (at the physician's office and pharmacy) to track awareness of the side effects statement and to determine to what extent consumers contact FDA to report a side effect.

(Response) The agency is in the process of implementing numerous safety initiatives under FDAAA that will benefit consumers. Section 906(a) of FDAAA requires published direct-to-consumer advertisements to include a statement encouraging reporting of negative side effects to FDA and providing the MedWatch Web site and phone number. Given that section 502(f)(2) of FDAAA likely will reduce the number of voluntary reports FDA receives on application OTC drug products as a result of this rule, we do not believe it is necessary to undertake an extensive educational campaign targeted at voluntary reporting for application OTC drug products at this time. However, should our experience with reporting under these new provisions indicate otherwise, we will consider whether educational efforts for the general public would be beneficial.

In addition, we note that the National Survey of Prescription Medicine Information Received by Consumers is not currently ongoing. If this survey is reinstated at a future date, we will consider adding specific questions relevant to the side effects statement at that time as suggested by the comment.

#### **IV. Analysis of Impacts**

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866

directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is not an economically significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the impact of the final rule will be proportional to sales volumes, the agency concludes that this final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

In accordance with Executive Order 12866, FDA has previously analyzed the potential economic effects of this final rule. We estimated that annualized costs of the proposed rule would be \$9.3 million to \$22.6 million (69 FR 21778 at 21783). For the final rule, we project that one-time costs will range from approximately \$38.0 million to \$49.6 million and annual costs will range from \$12.4 million to \$46.3 million. The total annualized impact of the final rule

will range from \$16.9 million to \$52.2 million with a 3-percent discount rate and from \$17.8 million to \$53.4 million with a 7-percent discount rate. We are unable to quantify the benefits of the final rule. Although the estimated costs of this final rule are higher than the estimated costs of the preliminary regulatory impact analysis, the agency has determined that the rule is not an economically significant regulatory action as defined by the order.

#### *A. Need for Regulation*

The BPCA required that the labeling of each drug approved under section 505 of the act be accompanied by a toll-free number and statement that the number is for reporting adverse events, not to receive medical advice. Because OTC drug products may be approved under section 505 of the act, we proposed that the labeling for all application OTC drug products include the side effects statement. Subsequently, FDAAA exempted any application OTC drug products whose packaging includes a toll-free number that consumers can call to report complaints to the manufacturer or distributor of the product. Consequently, to fulfill these statutory requirements, the final rule will require pharmacies and authorized dispensers to provide patients with the side effects statement with each dispensed prescription drug, and will require drug manufacturers to include the side effects statement in FDA-approved Medication Guides for drugs approved under section 505 of the act and in the labeling of application OTC drug products not subject to the exclusion in section 502(f)(2) of FDAAA.

#### *B. Costs of Regulation*

(Comment 22) Most comments on the costs of the proposed rule asserted that we understated the number of affected OTC drug products and the costs to modify OTC drug product labeling.

(Response) In most cases, however, changes under FDAAA made many of these comments irrelevant. As noted in this final analysis, we have updated the initial analysis with current numbers whenever possible.

## 1. Pharmacy Industry

a. *Number of affected pharmacies.* We received no comments on our initial estimate of the number of pharmacies affected by the requirement to include the side effects statement with each dispensed prescription drug. For the final analysis, we update the number of affected outlets with data from the 2002 Economic Census on the number of establishments that have merchandise sales from prescription drugs (table 1 of this document). Both retail and nonretail pharmacies may dispense prescription drugs to patients. Retail channels include independent drug stores, chain drug stores, mass merchants, grocery stores with pharmacies, and mail or Internet services. Nonretail channels include health maintenance organizations (HMOs), hospital outpatient pharmacies, offices of health care practitioners, and ambulatory care clinics.

The agency solicited comment on its assumptions about the percentages of affected dispensing locations currently distributing some form of printed CMI (69 FR 21783). Because no comments were received and the agency has no other information about pharmacy practices, we continue to assume that printed CMI accompanies: (1) 89 percent of the prescriptions dispensed by retail pharmacies, (2) 89 percent of prescriptions dispensed in ambulatory outpatient settings, and (3) 0 percent of prescriptions dispensed in other health care settings. Table 1 of this document shows the estimated number of affected outlets distributing CMI.

b. *Prescriptions dispensed.* Although information on the number of prescriptions dispensed by retail channels is publicly available, it is difficult

to estimate the number of prescriptions dispensed by nonretail channels. For the initial analysis of impacts, we used 2001 data from IMS Health to approximate the volume of prescriptions from nonretail channels. Based on the IMS data, nonretail channels dispensed from 6 percent to 18 percent of the prescription volume dispensed from retail channels (69 FR 21778 at 21784). Although we solicited comment on our estimate, we received no additional information. Thus, we assume that the percentage of prescriptions dispensed by retail and nonretail outlets remains similar to our initial estimate. In 2007, IMS Health estimated that retail channels dispensed approximately 3.8 billion prescriptions ([http://imshealth.com/vgn/images/portal/CIT\\_40000873/39/53/834329692007%20Channel%20Distribution%20by%20RXs.pdf](http://imshealth.com/vgn/images/portal/CIT_40000873/39/53/834329692007%20Channel%20Distribution%20by%20RXs.pdf)). We estimate that nonretail channels dispensed from 228 million (6 percent of 3.8 billion) to 671 million (18 percent of 3.8 billion) prescriptions, for a total volume of prescriptions in 2007 ranging from 4.0 billion (= 3.8 billion + 0.2 billion) to 4.5 billion (= 3.8 billion + 0.7 billion).

c. *Compliance costs for pharmacies.* For the initial analysis of impacts, we assumed that pharmacies currently distributing printed CMI would choose to comply with the requirements of the proposed rule by distributing the side effects statement in the CMI. We anticipated that the side effects statement could be added to existing pharmaceutical information databases used to produce CMI at a negligible one-time cost. Moreover, we assumed that periodic updates of other drug labeling information included in pharmaceutical databases required pharmacies or their computer system vendors to test the printing of the CMI on a regular basis. Because most pharmacies distribute printed CMI, we assumed that only pharmacies and authorized dispensers not

currently providing printed CMI would incur incremental costs to comply with the requirements of the proposed rule.

TABLE 1.—NUMBER OF PHARMACY OUTLETS WITH SALES OF PRESCRIPTION DRUGS AND DISTRIBUTING PRINTED CONSUMER MEDICATION INFORMATION (CMI)

Type of Outlet	Number of Outlets <sup>1</sup>	Number of Outlets Distributing CMI
<b>Retail outlets:</b>		
Pharmacy, drug, and health care stores	39,159	34,711
Food and beverage stores	20,227	18,002
Warehouse clubs and supercenters	2,553	2,502
Other general merchandise stores	5,469	4,867
Electronic shopping	88	78
Mail-order houses	365	325
Other direct selling establishments	26	23
<b>Nonretail outlets:</b>		
Offices of health practitioners	7,424	0
Hospital outpatient services	5,506	0
Clinics	3,117	2,774
HMOs	162	144
<b>Total outlets</b>	<b>84,096</b>	<b>63,427</b>

Sources: Retail outlets from table 1 of 2002 Economic Census, Retail Trade, Subject Series, publication number EC02-44SL-LS issued October 2005; Nonretail outlets from 2002 Economic Census, Health Care of Social Assistance, Subject Series, publication number EC02-62SL-LS issued October 2005.

<sup>1</sup> Includes establishments in the 2000 North American Industry Classification System (NAICS) industry codes 445, 446, 452, 454, 621, 622 that had sales from product line code 20161 (Prescriptions).

(Comment 23) We received one comment from a professional organization representing pharmacists that supported our assumption that most pharmacies will adopt the CMI option. One comment from a provider of pharmaceutical databases stated that it will not be difficult to include the side effects statement in the CMI. Two comments noted that in our initial analysis we did not take into account the one-time effort required to modify and test computer programs controlling the printing of the CMI and auxiliary labels, but provided no detailed information about these costs.

(Response) We agree that pharmacies choosing to distribute revised CMI (i.e., CMI with the side effects statement) will need to ensure proper printing of the side effects statement if they choose this option. Pharmacies that choose to print their own labels to affix on the dispensing container will incur costs to modify and test the computer programs that control the printing of auxiliary labels. However, we lack sufficient information about the percentage of pharmacies that would choose in-house printing of auxiliary labels to modify our initial estimate.

To illustrate the potential costs of the proposed rule, we estimated the level of effort required by a pharmacy to manually affix a sticker preprinted with the side effects statement on each prescription container. Because this option would cause a pharmacy to incur additional costs for each prescription drug dispensed, the agency believes that this would be a higher cost option for pharmacies and authorized dispensers that currently distribute printed CMI with prescription drugs.

(Comment 24) Two comments on the proposed rule stated that FDA failed to understand the workflow in a modern pharmacy and that manually affixing stickers would be more costly than we estimated.

(Response) We acknowledge that manually affixing a sticker in a highly automated system might cause disruptions in workflow that were not captured in our initial analysis. However, we have no other information that we could use to modify our estimate. Nevertheless, we have increased our cost estimate in the proposed rule by 35 percent to account for the following: (1) A 23-percent increase in the number of prescriptions and (2) a 12-percent increase in costs since 2003.<sup>1</sup> For pharmacies, the potential annual costs of the final rule in 2007 dollars will range from \$12.4 million to \$27.3 million. Similar to the range in the proposed rule, this range reflects uncertainty about the costs to affix the sticker to the prescription drug container, and the average number of prescriptions dispensed by affected pharmacy outlets.

## 2. Drug Manufacturers

We proposed to require that the labeling of application OTC drug products not subject to the exclusion in section 502(f)(2) of FDAAA include the OTC side effects statement in the warnings section of the drug facts format labeling.

<sup>1</sup> U.S. Department of Labor, Bureau of Economic Analysis, National Economic Accounts (<http://www.bea.gov/nationalnipaweb/SelectTable.asp?Selected=Y>).

For the analysis of the proposed rule, we predicted that manufacturers would spend \$3,000 per shelf-keeping unit (SKU) to modify the labeling of a new drug application (NDA) OTC drug product or \$1,000 per SKU to modify the labeling of an abbreviated new drug application (ANDA) OTC drug product. We assumed that each affected OTC drug product would have, on average, up to 3 SKUs. For the proposed rule, we estimated that approximately 1,570 OTC drug packages would need to be revised to add the side effects statement. Furthermore, we estimated manufacturers would need to add the side effects statement to about 18 Medication Guides.

a. *Number of affected products.* Although we received no comments on our estimate of the number of Medication Guides that would be revised, more prescription drugs have added Medication Guides since our initial estimate. Based on current agency information, we have increased our estimate from 18 to 370 Medication Guides.

(Comment 25) Comments from the drug industry and a member of Congress stated that FDA should not have included application OTC drug products in the proposed rule. Some comments expressed concern that because the labeling of most NDA OTC drug products includes a manufacturer's toll-free telephone number, addition of the MedWatch telephone number could confuse consumers. It was suggested that FDA exempt from the requirements of the proposed rule any OTC drug product whose labeling contains a toll-free number for the manufacturer or distributor.

(Response) The proposed rule would have required the same side effects statement on all application OTC drug products. As discussed previously in this preamble, the interim final rule codified section 502(f)(2) of FDAAA, which states that the requirement to include the side effects statement does

not apply to any OTC drug product approved under section 505 of the act if the product's packaging contains a toll-free telephone number through which consumers can report complaints to the manufacturer or distributor of the drug. Section 502(f)(2) of FDAAA thus creates a situation in which manufacturers and distributors of affected application OTC drug products will choose to either add the side effects statement or their own toll-free telephone number to OTC drug product labeling. Therefore, under the rule, the drug facts format labeling of application OTC drug products could vary depending on whether the affected manufacturer or distributor uses the side effects statement or its own toll-free number.

The agency previously estimated that certain retailers with more than 10 establishments would have some private label OTC drug products (62 FR 9046, February 27, 1997). Depending on the size of the firm, each private label OTC drug product could have numerous SKUs. Agency records indicate that there are about 60 unique application OTC products (i.e., a unique combination of active ingredient, dosage form, and strength). An informal convenience survey of stores in the Washington, DC, area and in northern New England looked at whether affected private label OTC drug product labeling contains a toll-free telephone number. We found that the packaging of most private label OTC drug products does not include a toll-free number for complaints.<sup>2</sup> It appears

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<sup>2</sup> FDA employees visited three mass merchants, three chain grocery stores, and four chain drug stores to roughly estimate the following: (1) The number of SKUs per private label OTC product for categories of products with high sales volumes and (2) the proportion of the labeling of these products including a toll-free telephone number. At each site, at least one private label ANDA OTC drug product from the following categories was examined to determine the number of SKUs for the product and the percentage of SKUs with a toll-free telephone number—allergy and asthma, antifungal, feminine hygiene, pain, stomach-diarrhea, and stomach-digestion. In addition, at some locations, employees examined private label ANDA OTC drug products for smoking cessation, lice control, hair restoration, and cold and sinus. We examined over 300 packages and found that the labeling of smoking cessation products and allergy and asthma eye drops already appear to include a toll-free telephone number. Excluding these products, only about 20 percent of the labeling of private label ANDA OTC products would conform to the requirements of the final rule without change. Finally, to estimate a range of products whose labeling would need to be modified, we

that most private label OTC drug product labeling will need to be modified to comply with the final rule. However, because most national brand OTC drug products affected by the rule already have a toll-free telephone number for complaints, current packaging for most national brand OTC drug products will conform to the requirements of the final rule without any further change.

For this final analysis, we assume that distributors of private label OTC drug products (i.e., the unique combination of active ingredient, dosage form, and strength) would not carry identical SKUs from different manufacturers. Although uncertain, the findings from our informal survey give us an idea of the number of private label OTC drug product SKUs that might be affected by the final rule. For the final analysis, therefore, we anticipate that any firm with 10 to 99 establishments will need to change the packaging of between 40 to 55 affected private label OTC drug products and any firm with 100 or more establishments will need to change the packaging of between 110 to 135 private label OTC drug products. Table 2 of this document illustrates the number of possible firms that could have private label OTC drug products.

TABLE 2.—ESTIMATE OF THE NUMBER OF PRIVATE LABEL DISTRIBUTORS

Kind of Business	Number of Firms With 10–99 Establishments	Number of Firms With 100 or More Establishments
Supermarket and other grocery	194	37
Pharmacy, drug, and proprietary stores	59	16
Warehouse clubs and supercenters	3	6
Total	256	59

Source: Data for NAICS numbers 445110, 4461101, 4461102, and 45291 from table 3 of 2002 Economic Census, Retail Trade, Subject Series, Establishment and Firm Size (Including Legal Form of Organization), publication number EC02-44SS-SZ issued November 2005.

*b. Cost to modify product labeling.*

(Comment 26) We received three detailed comments that included alternative estimates of the cost to revise NDA OTC drug product labeling. No

adjusted the average number of SKUs for each product (i.e., active ingredient, dosage form, and strength) by the proportion of SKUs with labeling including a toll-free telephone number.

comments were submitted on our estimate of the cost to revise ANDA or private label OTC drug product labeling or Medication Guides.

(Response) To account for inflation, we updated our estimate of the cost to revise a Medication Guide from \$4,177 to \$4,500 (2007 dollars) for an NDA prescription drug and from \$1,580 to \$1,800 (2007 dollars) for an ANDA prescription drug. The total one-time cost to add the side effects statement to Medication Guides will be \$990,000 (= 120 Medication Guides x \$4,500 + 250 Medication Guides x \$1,800).

In recent years some large retailers have developed a single nationwide private label brand for all of their private label OTC drug products.<sup>3</sup> When comparing like OTC drug products, consumers could perceive a difference in the safety of the private label OTC drug products if the private label OTC drug product packaging displays the side effects statement instead of a manufacturer's toll-free number, such as is found on most innovators' branded products. Economic theory predicts that any labeling change which signals a decrease in product quality will be balanced by a decrease in the demand for the product. Large retailers will weigh the additional costs associated with the addition of their toll-free number on their OTC drug product packaging against the monetary value of the perceived decrease in product quality that could be signaled by the addition of the side effects statement. Private label retailers will choose to include their own toll-free telephone number instead of the side effects statement if they believe that the side effects statement will decrease the perceived quality of their products more than the cost to add the toll-free telephone number.

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<sup>3</sup> "Consolidated Medicine," January/February 2005, Private Label Magazine, at <http://www.privatelabelmag.com>.

We have increased our estimate of the cost to modify the labeling of private label OTC drug products from \$1,000 per SKU to \$2,140 per SKU. As shown in table 3 of this document, private label distributors might spend from \$36.4 million to \$47.9 million in one-time costs to modify drug labeling to include a telephone number or side effects statement. In addition, each distributor might spend up to 40 hours deciding whether to include its own toll-free telephone number at a one-time cost of \$640,000 (= 320 distributors x \$50 per hour x 40 hours), for total one-time costs ranging from \$37.0 million to \$48.6 million.

We expect that there would be some impact of the toll-free telephone number on the workload of private label distributors who choose to add their own toll-free telephone number. Although this impact is uncertain, distributors may need to hire up to one full-time employee (FTE) at a cost of about \$53,500<sup>4</sup> to answer additional telephone calls generated by the addition of their toll-free telephone number on private label OTC drug product packaging. If the incremental increase in telephone calls is minimal, distributors will not incur these costs. However, if all 320 distributors incurred this incremental expense, it will cost the pharmacy industry an additional \$17.1 million dollars annually. In total, the final rule will cost drug manufacturers or private label distributors from \$4.5 million to \$22.9 million annualized at a 3-percent discount rate and from \$5.4 million to \$24.2 million annualized at a 7-percent discount rate.

### 3. Burden on FDA

(Comment 27) Several comments stated that the side effects statement would increase the volume of non-serious calls to MedWatch and potentially dilute the value of direct adverse event reports.

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<sup>4</sup> U.S. Department of Labor, Bureau of Labor Statistics, Occupational Employment and Wages, May 2007 (<http://www.bls.gov/oes/current/oes292052.htm>).

(Response) In our initial analysis, we were uncertain about the burden this rule would place on FDA. Although we are still uncertain about the burden of the final rule, the results of our Internet study are encouraging. Most people understood the meaning of the side effects statement and understood that the FDA toll-free number was intended only to report serious side effects. Participants in the study showed little inclination to use the FDA toll-free number and would be more likely to expect their health care provider to report side effects. Without other information, we leave our initial analysis of the FDA burden unchanged.

#### 4. Summary of the Impacts of the Final Rule

Table 4 of this document summarizes the costs of the final rule. The total annualized impact of the final rule will range from \$16.9 million to \$52.2 million with a 3-percent discount rate and from \$17.8 million to \$53.4 million with a 7-percent discount rate. Most of this cost will likely be passed on to consumers. Even though the total annualized costs are uncertain, they are significantly below the threshold of an economically significant rule. Moreover, the final rule gives pharmacies flexibility to select the option that is least burdensome for their individual business situation and fulfills the statutory requirements of the BPCA and FDAAA. Finally, these costs represent a small proportion of affected product sales.

TABLE 3.—ESTIMATED COST TO MODIFY PRIVATE LABEL OTC LABELING

Type of Distributor	Number of Distributors	Estimate of the Number of Private Label SKUs		Number of Affected SKUs		Cost to Revise OTC Labeling (\$ million)	
		Low	High	Low	High	Low	High
Small	260	40	55	10,400	14,300	22.3	30.6
Large	60	110	135	6,600	8,100	14.1	17.3
Total	320			17,000	22,400	36.4	47.9

TABLE 4.—COST SUMMARY

Affected Sector	One-Time Cost (\$ mil)		Annual Costs (\$ mil)		Annualized at 3% (\$ mil)		Annualized at 7% (\$ mil)	
	low	high	low	high	low	high	low	high
Retail and nonretail pharmacies			12.4	27.3	12.4	27.3	12.4	27.3
Drug manufacturers and private label distributors	38.0	49.6	0.0	17.1	4.5	22.9	5.4	24.2
FDA			0.0	1.9	0.0	1.9	0.0	1.9
Total	38.0	49.6	12.4	46.3	16.9	52.2	17.8	53.4

### *C. Benefits of Regulation*

(Comment 28) One comment from an organization representing drug manufacturers stated that the proposed rule had no obvious benefits and in contrast could have a detrimental effect on adverse event reporting and detection.

(Response) The agency agrees that the benefits of this rule are uncertain. As described elsewhere in this preamble, the results of our Internet labeling comprehension study suggest that most consumers understand the side effects statement and would be unlikely to call FDA. Even if they experienced a serious side effect, most participants indicated that they would contact their health care provider and would assume that he or she would report their side effect to FDA. If the final rule increases reports of serious side effects by health care providers, it might aid the agency's efforts to monitor the postmarket safety of drug products.

### *D. Final Regulatory Flexibility Analysis*

We received no comments that would change our initial analysis of the impacts on small entities. Most impacts on small entities represent a small proportion of sales and the rule would probably have a minimal effect on even the smallest entities. For our initial analysis, we estimated that adding a preprinted sticker to each prescription container would cost about \$.03 per prescription and could reduce a retail pharmacy's average revenues by about

0.3 percent. For the final analysis, we adjust the per prescription cost of the sticker option by 12 percent, increasing the cost of this option to approximately \$0.04 per prescription. The National Association of Chain Drug Stores (NACDS) reports that in 2007 the average cost of a retail prescription was \$69.91. Retail pharmacies received about 17 percent or an average of \$13.17 for each prescription.<sup>5</sup> At current revenue levels, the average cost for small pharmacies to comply with the final rule will still be about 0.3 percent of the average per-prescription revenue.

The costs for private label distributors were not included in the initial analysis. However, all distributors large enough to maintain private labels have annual sales above the SBA size standards. Because many of the impacts of the final rule are uncertain, we are not able to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

#### **VI. Paperwork Reduction Act of 1995**

This regulation imposes no new collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### **VII. Environmental Impact**

The agency has determined under 21 CFR 25.30(h) 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.

#### **VIII. Federalism**

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have

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<sup>5</sup> <http://www.nacds.org/wmspage.cfm?parm1=507#pharmpricing>.

a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to “construe \* \* \* a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” Section 751 of the act (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act provides that “\* \* \* no State or political subdivision of a State may establish or continue in effect any requirement—(1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*).” Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. Section 751(b) through (e) of the act outlines the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.

Even where the express preemption provision is not applicable, implied preemption may arise. *See Geier v. American Honda Co.* 529 U.S. 861 (2000). Under the principles of implied conflict preemption, courts have found State law preempted where it is impossible to comply with both Federal and State law or where the State law “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.” *See English v. General Electric Co.*, 496 U.S. 72, 79 (1990); *Florida Lime & Avocado Growers, Inc.*, 373 U.S. 132, 142–43 (1963); *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

This rule amends the labeling requirements for certain application OTC drug products to require the addition of a side effects statement, and to require pharmacies and authorized dispensers to distribute the side effects statement with each prescription drug approved under section 505 of the act and dispensed. This rule would have a preemptive effect to the extent that a State requires labeling that directly conflicts with, is different from, or is in addition to, the side effects statement required by this rule for certain application OTC drug products. This preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. The rule would also have a preemptive effect to the extent that a State imposes requirements on pharmacies or authorized dispensers that conflict with the requirements of this rule or frustrate the federal purpose with respect to distribution of the side effects statement. Preemption with respect to these requirements is consistent with the doctrine of implied conflict preemption. FDA believes that the preemptive effect of the final rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that “when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.” FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule (69 FR 21778). FDA received no comments from any States on the proposed rulemaking. On January 3, 2008, FDA published an interim final rule codifying the proposed rule which, under FDAAA, became

effective by operation of law on January 1, 2008 (73 FR 402). FDA received no comments from any State on the interim final rule.

In addition, on July 31, 2008, the FDA Division of Federal and State Relations provided notice via fax and e-mail transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for comment on the rule. It advised the States of the publication of the proposed rule and interim final rule and encouraged State and local governments to review the notice and interim final rule to provide any comments to Docket No. FDA-2003-N-0313 (formerly Docket No. 2003N-0342) opened in the April 22, 2004, **Federal Register** proposed rule, by a date 30 days from the date of the notice (i.e., by August 31, 2008, or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in Docket No. FDA-2003-N-0313.

In conclusion, FDA believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

(FDA has verified all Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, the interim final rule amending 21 CFR parts 201 and 208 and adding 21 CFR part 209, which was published at 73 FR 402 (January 3, 2008), is adopted as a final rule without change.

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Joyce  
Shure  
10/22/08

Dated: October 21, 2008.

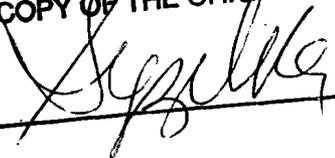


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Jeffrey Shuren,  
Associate Commissioner for Policy and Planning.

[FR Doc. 08-????? Filed ??-??-08; 8:45 am]  
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