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21 CFR Parts 314, 601, and 814

[Docket No. FDA–2008–N–0032] (formerly Docket No. 2008N–0021)

RIN 0910–ZA32

Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

9/22/08

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations regarding changes to an approved new drug application (NDA), biologics license application (BLA), or medical device premarket approval application (PMA). This final rule provides that a supplemental application submitted under certain FDA regulations is appropriate to amend the labeling for an approved product to reflect newly acquired information and to add or strengthen a contraindication, warning, precaution, or adverse reaction if there is sufficient evidence of a causal association with the drug, biologic, or device, as defined in other FDA regulations and guidance documents.

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

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of January 16, 2008 (73 FR 2848), FDA proposed amending its regulations regarding changes to an NDA, BLA, or PMA to codify the agency's longstanding view concerning when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change (the January 2008 proposed rule). With respect to drugs, § 314.70(c)(6)(iii) (21 CFR 314.70(c)(6)(iii)) provides that certain labeling changes related to an approved drug may be implemented upon receipt by the agency of a supplemental new drug application (sNDA) that includes the change. The corresponding regulation for biological products, § 601.12(f)(2) (21 CFR 601.12(f)(2)), provides that products with certain labeling changes may be distributed before FDA approval. Similarly, with respect to devices, § 814.39(d) (21 CFR 814.39(d)) provides that certain labeling changes may be placed into effect upon submission of a PMA supplement, but prior to the sponsor's receipt of a written FDA order approving the supplement. The supplements described by §§ 314.70(c), 601.12(f)(2), and 814.39(d) are commonly referred to as "changes being effected supplements" or "CBE

supplements."[1] FDA proposed amending these provisions to affirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and to make it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or medical device. The phrase "sufficient evidence of a causal association" refers to the standards for drugs and biologics described in § 201.57(c)(6) (21 CFR 201.57(c)(6)) (for Warnings and Precautions—"reasonable evidence"), and in § 201.57(c)(7) (21 CFR 201.57(c)(7)) (for Adverse Reactions—"some basis to believe") and to the standard for devices in the Device Labeling Guidance, General Program Memorandum G91–1 (March 8, 1991) (*http://www.fda.gov/cdrh/g91-1.html*) ("reasonable evidence") for the level of evidence needed to support a causal association with these medical products.

As described in the January 2008 proposed rule, FDA believes that amending FDA's CBE regulations is consistent with the agency's role in protecting the public health. Before approving an NDA, BLA, or PMA, FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS Act), and FDA regulations, the agency makes approval decisions, including the approval of supplemental applications, based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling. See, e.g., 21 U.S.C. 355(d); 42 U.S.C. 262; 21 U.S.C.

[1] For devices, such supplements are also referred to as Special PMA Supplements. This document will use the term "CBE supplement."

360e(d)(2). FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will help to ensure that scientifically accurate information appears in the approved labeling for such products.

II. Changes to the January 2008 Proposed Rule

FDA has made the following changes to the January 2008 proposed rule:

The definition of "newly acquired information" has been revised to clarify that data, whether derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) needs to be of a "different type or greater severity or frequency than previously included in submissions to FDA". The codified section of the January 2008 proposed rule suggested that this limitation applied only to data derived from reports of adverse events. Instead, it applies to data derived from new clinical studies, reports of adverse events, and new analyses of previously submitted data.

In addition, FDA has made one technical correction to the January 2008 proposed rule. The technical correction is in § 601.12, where an amendment was proposed adding paragraph (f)(5), containing the definition of "newly acquired information." In fact, the amendment should have proposed adding this definition to paragraph (f)(6) of § 601.12 rather than to paragraph (f)(5) of § 601.12.

III. Comments

FDA received approximately 20 comments to the January 2008 proposed rule. The comments were submitted by consumer advocacy groups,

individuals, law firms, law professors, pharmaceutical companies, trade associations, and Members of Congress.

(Comment 1) Several comments stated that this proposed amendment would make it more difficult for sponsors to warn about new risks. Most of these comments were focused on the aspect of the rule that imposed a requirement that sponsors have a sufficient amount of causal evidence before a CBE should be used.

In addition, comments argued that FDA should distinguish between situations when sponsors are obligated to warn of a new risk, and situations when the sponsor is permitted to warn. For example, some comments stated that the requirement in § 201.57(c)(6) that there be some evidence of a causal relationship should apply to situations when a manufacturer must warn, but should not apply to when manufacturers may warn. These comments argue that public policy should not discourage sponsors from warning, even when the regulations do not require it.

Similarly, one comment argued that causation is not a binary issue (i.e., causation is either present or not). Rather, the causal relationship between a product and an adverse effect is often difficult to establish and may require large trials, often specifically designed to assess the risk. One comment argued that because of this difficulty, drug and device sponsors may delay warning and delay making labeling changes by asserting that the CBE regulation (if finalized as proposed) would not permit them to amend their labeling.

FDA does not agree that this rule will make it more difficult to provide appropriate warnings regarding hazards associated with medical products. This rule is intended to describe FDA's existing labeling standards and policies, but does not amend the standards under which sponsors must provide warnings

regarding risks (§ 201.57(c)(6)). Nor is the rule intended to suggest that there is a mathematically precise distinction between whether there is, or is not, sufficient evidence of a causal relation between a drug and an adverse effect to support its inclusion in the labeling. The rule is, nevertheless, sufficiently clear and objective to allow sponsors to determine whether a medical product's labeling should be amended. If new safety information meets the requirements of § 201.57(c)(6), it is appropriate for inclusion in the labeling of a drug or biologic and a sponsor must update its labeling "as soon as" such information becomes available. That section states that causation need not have been "definitely established" for a warning to be required to appear in labeling, but rather that there need only be "reasonable" evidence of a causal association with the drug, a standard that could be met by a wide range of evidence. A CBE submission may be made when the evidence meets the standard set forth in this rule, even if that evidence would not also support a higher evidentiary standard, such as a finding that there is a "preponderance" of evidence that a product actually causes a particular kind of adverse event. A sponsor's submission or FDA's acceptance of a CBE supplement does not necessarily mean that a drug product actually has caused any particular adverse event or type of adverse event.

Through § 201.57 (and the predecessor regulation, now codified at § 201.80 (21 CFR 201.80)), the agency set uniform standards for drug labeling, seeking to ensure that scientifically sound information is provided in the labeling of the drug. There is no reason the standard for adding new information to labeling should be different from the standard for the initial labeling. If new information about a drug comes to light, a sponsor must make a decision as to whether the requirements of § 201.57 are met, and whether to submit a CBE

supplement or other type of supplemental application. Failure to update labeling as required could result in regulatory actions or criminal penalties. If there is doubt as to whether the standard of § 201.57(c)(6) has been met, a sponsor should confer with FDA. The agency has clarified by regulation and guidance the types of supplements that should be filed to satisfy a sponsor's obligations to change a drug's labeling, and sponsors can consult with FDA on that question as well. *See* 21 CFR 314.70; Guidance for Industry: Changes to an Approved NDA or ANDA (November 1999) (*http://www.fda.gov/cder/guidance/2766fnl.pdf*).

This rule does not undermine a sponsor's responsibility to maintain its label—rather, it clarifies FDA's longstanding practice of requiring that sponsors must have sufficient evidence that the standards are met (§ 201.57(c) and Device Labeling Guidance).

With respect to comments suggesting that § 201.57 sets the standard for when sponsors must warn, but that a lower standard should be used under § 314.70(c)(6) for when a sponsor may warn, FDA has previously stated and reiterates here that it "interprets the Act to establish both a 'floor' and a 'ceiling', such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading" (71 FR 3922 at 3935, January 24, 2006) (the 2006 Physician Labeling Rule). FDA, therefore, declines to set different standards for when a sponsor must warn, as opposed to when it may warn of a particular risk or adverse event.

(Comment 2) Several comments stated that the rule would conflict with the intent of Congress. FDA in no way believes that this rule conflicts with Congressional intent. Another, comment stated that Congress did not intend

for the act to preempt State law because there is no express preemption provision with respect to drugs. Several comments referred to the recently enacted Food and Drug Administration Amendments Act of 2007 (FDAAA) in support of this position. These comments suggest that for FDA to change the circumstances when sponsors could update their labeling by a CBE would conflict with congressional intent. FDAAA provided additional authority for FDA to require sponsors to make safety related changes to their labeling. The statute also included a rule of construction as part of a paragraph providing new authority to the Secretary to require labeling changes for drug products: "This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." (Section 505(o)(4)(I) of the act (21 U.S.C. 355(o)(4)(I))).

FDA does not believe that the absence of an express preemption provision with respect to drugs affects the application of the doctrine of implied preemption. Furthermore, FDA does not agree that the rule of construction affects FDA's ability to finalize the January 2008 proposed rule for several, independent reasons.[2] The January 2008 proposed regulation is consistent with the rule of construction. First, the rule of construction, by its terms, contemplates amendments to applicable regulations by its reference to "successor regulations" governing a sponsor's obligation to change product labeling. Congress, therefore, expressly acknowledged that FDA's regulations are not static and may be subsequently amended by the agency, as FDA is

[2] FDA notes that the rule of construction in 21 U.S.C. 355(o)(4) on its face does not relate to medical devices.

doing here. Second, the rule of construction operates to preserve Federal labeling obligations only in the face of an argument that "this paragraph"—21 U.S.C. 355(o)(4), the new statutory provision permitting the Secretary of Health and Human Services (the Secretary) to impose labeling changes after meeting certain procedural requirements—"affects" those responsibilities. Third, the rule of construction refers to, and therefore preserves only a sponsor's Federal-law (as opposed to State-law) "responsibility[ies] * * * to maintain its label." As was noted in the U.S. Government's amicus brief at the merits stage in *Wyeth* v. *Levine*, No. 06–1249 (June 2008) (*http://www.justice.gov/osg/briefs/2007/3mer/1ami/2006-1249.mer.ami.pdf*), the rule of construction "simply means that the relevant amendments do not affect obligations under other *federal* laws. It does not manifest any intent to depart from the application of ordinary principles governing the preemption of conflicting *state* laws. * * * [T]he text of the rule of construction that Congress actually enacted, which is limited to the effect of Section 901, itself preserves *complementary federal* requirements without evincing any intent to protect *conflicting state* laws." *Id.* at 32 (emphases in original).

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

In other words, the rule of construction makes it clear that a sponsor cannot contend that, because the Secretary has the power to order new labeling changes, the sponsor no longer has an obligation to monitor post-marketing experiences and maintain its labeling under applicable Federal regulations. Indeed, it can maintain its labeling by using all existing tools, including through prior approval supplements, CBE-30 day supplements (§§ 314.70(c),

601.12(c) and 814.39(e)), and CBE supplements, along with other changes that may be reported in an annual report. Under both the rule of construction and this final rule, a sponsor still must update its labeling under Federal law "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug" (§ 201.57(c)(6)), and add other risk information as required by the regulations (§ 201.57(c)).

If FDA were to interpret section 505(o)(4) of the act as eliminating the ability or obligation under Federal law of a sponsor to "maintain" its label, this would conflict with the rule of construction. But this final rule does not take away a sponsor's obligation to maintain its labeling under Federal law under appropriate circumstances. FDA is amending the text of the rules at issue here not because of the new powers in section 505(o)(4) of the act, but to clarify a sponsor's responsibilities and to make the text of the regulations match FDA's practice regarding CBE labeling changes, which predate FDAAA. Manufacturers continue to have a responsibility under Federal law, including the amended regulations under this rulemaking, to maintain their labeling and update the labeling with new safety information.

(Comment 3) One comment asserted that this rule could undermine consumer confidence in medical products and FDA. Consumer confidence in medical products and in FDA itself is critically important. This amendment is intended to clarify FDA's existing policies and is intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, and to prevent overwarning, which may deter appropriate use of medical products, or overshadow more important warnings. Accordingly, FDA does not agree that the rule will undermine confidence in medical products or the agency.

(Comment 4) One comment stated that the January 2008 proposed rule's reference to "newly acquired information" might undermine warnings in situations where a sponsor warns about a particular risk, but then later information demonstrates that the warning was insufficient.

FDA believes that the final rule addresses this concern. First, if later data or analyses demonstrate that prior warnings were insufficient, such data would clearly qualify as newly acquired information under the rule. Indeed, the rule expressly provides that new analyses of previously submitted information are considered new information that could be submitted by a CBE supplement (provided that other requirements for a CBE supplement are met). Therefore, if a sponsor determined that existing warnings were insufficient based on newly acquired information such as a new analysis of previously submitted data, the sponsor could still submit a CBE based on its new analysis of the previous data, provided the other requirements of the rule are met. Moreover, FDA now has new tools to address this situation, including its authority to require labeling changes under section 505(o) of the act.

(Comment 5) Several comments asserted that sponsors, not FDA, have the most information about their products and should have authority to revise their labeling as soon as new information comes to light.

Sponsors are still required to act promptly to add risk information to labeling (§ 201.57(c)(6)). This rule describes the standard for one type of change to the labeling. It is intended to clarify the circumstances in which sponsors are required to update labeling, not to undermine or remove a sponsor's obligation to modify labeling to reflect appropriate new information. Under FDA's regulations and this final rule, sponsors are required to warn as soon as appropriate new information comes to light (§ 201.57(c)(6)).

(Comment 6) Several comments stated that FDA did not have sufficient resources to review all potential warnings before labeling may be updated. As stated in the January 2008 proposed rule, FDA does not consider this amendment to substantively change the standards for submission of CBE or prior review supplements. The agency does not expect that it will increase the number of prior approval supplements or otherwise increase agency workloads.

(Comment 7) One comment requested that FDA clarify the relationship between the January 2008 proposed rule and statements made by FDA in the preamble to the 2006 Physician Labeling Rule (71 FR 3922). The comment inquired whether these changes "supersede" certain statements in the preamble to the 2006 Physician Labeling Rule. The agency believes that these amendments are consistent with prior statements by FDA, including those in the 2006 Physician Labeling Rule. The preamble to the 2006 Physician Labeling Rule set forth a number of principles regarding FDA's regulation of drug labeling. See, e.g. 71 FR 3922 at 3935 ("FDA interprets the act to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act" * * *); ibid. ("State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products * * *"). That preamble also set forth some non-exclusive examples of instances of preemption. Id. at 3935–3936 (stating that "at least" the enumerated cases are preempted). In a proposed rule that published in the **Federal Register** of May 29, 2008 (73 FR 30831 at 30861), FDA reiterated its support for the general principles underlying preemption set forth in the 2006 Physician Labeling Rule. In briefs

recently filed in the Supreme Court of the United States and in testimony before Congress, FDA has also stated a more generally applicable rule that is consistent with the examples of preempted cases and the principles set forth in the preamble to the 2006 Physician Labeling Rule that: (1) The labeling requirements are not a mere minimum safety standard, but rather strike a balance between risks and benefits, and (2) FDA's regulations permit changes in labeling without prior approval only in narrow circumstances. Specifically, FDA has explained that State law claims that "challenge labeling that FDA approved after being informed of the relevant risk" are preempted. Brief of the United States as Amicus Curiae Supporting Petitioner, *Wyeth* v. *Levine*, No. 06–1249; Testimony of Deputy FDA Commissioner Randall Lutter before The House Committee on Oversight and Government Reform 5 (2008) *http://oversight.house.gov/documents/20080514142253.pdf* ("* * * State law claims are preempted if they challenge a design or labeling that FDA approved, after being informed of the relevant health risk * * *"). FDA reiterates and reaffirms here the positions set forth in those documents. FDA further notes that FDA there explained the interplay between this CBE regulation and preemption. FDA believes that this explanation sufficiently describes the relationship between this CBE regulation and the 2006 Physician Labeling Rule preamble.

(Comment 8) One comment requested that FDA make it clear that information previously known to the manufacturer, but not submitted to FDA, can be eligible for inclusion in a CBE amendment.

The term "newly acquired information" is defined in the final rule as "information not previously submitted to FDA * * *." Accordingly, if information was previously known to the manufacturer, but not submitted to

FDA, it would be "newly acquired information" that may qualify for inclusion in a CBE supplement (provided other requirements for a CBE supplement have been met).

(Comment 9) Several comments requested that FDA clarify the effect of this amendment on State tort liability and preemption, and one comment stated that this rule lacked a sufficient statement of irreconcilable conflict to justify the agency's assertion of implied preemption of "all [S]tate law". This rule does not preempt all State tort law and, furthermore, an "irreconcilable conflict" (i.e., an impossibility of compliance with both Federal and State law) is not the only basis for preemption of State law. Under implied preemption principles, if a State law frustrates Federal objectives, the State law is preempted. As a result, FDA's views on preemption, as explained elsewhere in this preamble, are amply justified by well-established principles of preemption. See *Geier* v. *American Honda Co.*, 529 U.S. 861 (2000); *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). Moreover, liability imposed under State tort law constitutes a State "requirement" within the meaning of 21 U.S.C. 360k(a). See *Reigel* v. *Medtronic*, 128 S.Ct. 999, 1008–09 (2008). For further discussion of the scope of preemption, see the response to comment 7 of this document and section VIII. Federalism of this document.

(Comment 10) One comment requested that FDA develop an alternative mechanism to address proposed labeling changes. FDA believes that its regulations (as modified in this final rule) provide appropriate and adequate regulatory pathways for updating and modifying labeling of drugs, biological

products, and medical devices. See § 314.70(c) (for drugs), § 601.12(f)(2) (for biological products) and § 814.39(d) (for medical devices).

(Comment 11) One comment requested that FDA clarify the degree of certainty that is required for demonstrating causation under FDA's regulations. FDA does not believe that additional clarification of its labeling rules is necessary. The regulations set forth in § 201.57 provide relevant standards for when information is appropriate for inclusion in labeling, including causation standards. FDA believes that standard is sufficiently clear and objective.

(Comment 12) One comment noted that the preamble to the January 2008 proposed rule stated that "FDA intends to consider information 'newly acquired' if it consists of data, analyses, or other information not previously submitted to the agency, *or submitted within a reasonable time period prior to the CBE supplement* * * *." (73 FR 2848 at 2850) (emphasis added). The comment requested that FDA clarify the temporal relationship between the submission of new information to FDA and a subsequent CBE supplement. FDA agrees that this issue should be clarified here so as to provide greater guidance to sponsors in determining their regulatory obligations. Newly acquired information includes information not previously submitted to FDA. If a sponsor submits data or analysis to FDA as part of a discussion of the kind of labeling change that would be appropriate and decides as a result of that discussion to prepare and submit a CBE supplement, then the supporting data or analysis will not be considered "previously submitted to FDA"—even if it was not first submitted on the same day as the CBE supplement. This allows for a labeling change when a sponsor submits data or analysis to FDA before the sponsor has completed its CBE supplement, and is also designed so as not to deter the sponsor from submitting the information for fear that

such a submission would preclude the sponsor from making a CBE change. This clarification is designed to address the situation where a sponsor submits data or analyses to FDA as part of the process of determining what labeling change is appropriate, and then diligently and promptly prepares a CBE supplement.

Moreover, FDA also notes that the definition of "newly acquired information" includes "new analyses" of previously submitted information. If a sponsor submits information to FDA, then later conducts a new analysis that demonstrates that labeling should be revised to account for that information, a CBE would be appropriate. For example, if the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for "newly acquired information".

(Comment 13) One comment requested that FDA clarify the relationship between the CBE regulations and risk evaluation and mitigation strategies (REMS) for drugs and biological products.

Under the new authority provided in FDAAA, FDA may require the submission of a proposed REMS if FDA believes that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks. A REMS must be approved by FDA (21 U.S.C. 355–1(h)), as must proposed modifications to a REMS (21 U.S.C. 355–1(g)). Accordingly, if the labeling for a drug describes an element of an approved REMS, the sponsor must receive prior approval of any labeling changes that would necessitate a change to the sponsor's REMS. For example, if a REMS included elements to assure safe use under section 505–1(f) of the act, some of those elements might be described

in the approved labeling for the drug or biologic. If the sponsor became aware of newly acquired safety information that would otherwise be appropriate for a CBE, but would require the sponsor to modify an element to assure safe use that is required under a REMS, the sponsor would need to receive prior approval of the labeling change. However, if the newly acquired information is related to the concern leading to a REMS but the proposed change to labeling could be made without requiring a modification of the REMS, the approved labeling for the product could be strengthened without prior approval. For example, if a REMS was imposed requiring periodic monitoring of liver enzymes to ensure the risk of liver toxicity for a drug was outweighed by the benefits of the drug, strengthening warnings related to that risk may be made by a CBE supplement (provided that other requirements for a CBE supplement are met and that the change can be made without modifying the REMS).

(Comment 14) One comment requested that FDA clarify that any change to the Highlights section of the labeling of a drug or biologic must be made by a prior approval supplement.

The agency agrees that this issue should be clarified, but does not agree that changes to Highlights can never be accomplished by a CBE supplement. Under existing regulations, changes to the Highlights are classified as a "major change," requiring a prior approval supplement (§ 314.70(b)(2)(v)(C)). Accordingly, in most cases, changes to Highlights will require a prior approval supplement. However, in the preamble to the January 2008 proposed rule, we noted that FDA could waive this limitation under § 314.90 or request that a sponsor make a change to Highlights under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(E). These provisions authorize FDA to waive the Highlights

limitation or otherwise ask the sponsor to submit a CBE supplement in appropriate circumstances.

(Comment 15) One comment requested that FDA clarify that sponsors may not use the CBE process to submit labeling changes for drugs or biological products under section 505(o) of the act.

FDA disagrees with this comment. Under section 505(o) of the act, FDA must notify the sponsor if the agency becomes aware of new safety information that should be included in the labeling for a particular drug or biologic. Following that notification, the sponsor must submit a "supplement" proposing changes to the labeling or submit a statement explaining the reasons why the sponsor believes the labeling change is not warranted. Nothing in section 505(o) limits this "supplement" to a prior approval supplement. In fact, to effect the change most rapidly, FDA may request that the sponsor file a CBE supplement under these circumstances.

(Comment 16) One comment requested that FDA provide a comprehensive, written response to every CBE supplement submitted to the agency by a sponsor, describing FDA's grounds for approval, disapproval, or, as the case may be, request for modification to the submitted CBE supplement. FDA disagrees with this comment. The comment failed to provide a compelling justification for this proposal.

(Comment 17) One comment asserted that if FDA finalizes this rule, it will create a disincentive for sponsors to conduct additional trials of their products because the sponsors would have to provide additional warnings if causation is shown. Under current regulations, sponsors must warn about risks of approved products if the requirements for updating labeling are triggered. This

rule does not change those standards. FDA therefore does not believe that it will change the incentives for sponsors to conduct new clinical trials.

(Comment 18) One comment stated that the rule would unjustifiably impose an added regulatory burden. FDA disagrees with this comment, as this rule does not add to the existing regulatory burden. Rather, as previously stated, the rule simply affirms that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and makes it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or medical device. For further discussion of the regulatory burden, see sections V. Analysis of Impacts and VI. Paperwork Reduction Act of this document.

IV. Legal Authority

As explained in the January 2008 proposed rule, FDA's legal authority to modify §§ 314.70, 601.12, and 814.39 arises from the same authority under which FDA initially issued these regulations. The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*) and the Public Health Service Act (42 U.S.C. 201 *et seq.*) provide FDA with authority over the labeling for drugs, biological products, and medical devices, and authorize the agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for such products.

Section 502 of the act (21 U.S.C. 352) provides that a drug, biologic,[3] or medical device will be considered misbranded if, among other things, the labeling for the product is false or misleading in any particular (21 U.S.C. 352(a)). Under section 502(f) of the act, a product is misbranded unless its

[3] Although the language of section 502 of the act refers only to drugs and devices, it is also applicable to biologics. (See 42 U.S.C. 262(j)).

labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage or methods or duration of administration or application. Moreover, under section 502(j) of the act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505 of the act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Similarly, under section 515(d)(2) of the act (21 U.S.C. 360e(d)(2)), FDA must assess whether to approve a PMA according to the "conditions of use prescribed, recommended, or suggested in the proposed labeling" of the device. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Section 351 of the PHS Act (42 U.S.C. 262) provides additional legal authority for the agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent (42 U.S.C. 262(a)). Section 351(b) of the PHS Act (42 U.S.C. 262(b)) prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, 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 a significant regulatory action as defined by 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 these amendments to existing regulations are intended only to codify the agency's interpretation of current policy, the agency certifies that the 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.

The objective of the final rule is to make explicit the agency's view of when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review of the change. More specifically, the purpose of the final rule is to clarify that a CBE supplement

is appropriate to amend the labeling for an approved product only to reflect newly acquired information, and to clarify that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is reasonable evidence of a causal association with the approved drug, biologic, or medical device. FDA does not consider this to be a substantive policy change, and it does not alter the agency's current practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.

Because this final rule does not establish any new regulatory or recordkeeping requirements, the agency does not expect that there will be any associated compliance costs. The final rule simply clarifies the agency's interpretation of when sponsors are allowed to add information regarding the risks associated with a product to the labeling without prior approval from FDA. It is expected that these clarifications will promote more effective and safe use of approved drug, biologic, and medical device products. The agency believes that any potential impacts of these amendments to existing regulations will be minimal because this action does not represent a substantive change from current policy. We did not receive any comments on the January 2008 proposed rule that would cause us to reconsider these determinations.

VI. Paperwork Reduction Act of 1995

This final rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 35013520). The collections of information in 21 CFR part 314 have been approved under OMB Control No. 0910–0001 (expires May 31, 2011); 21 CFR part 601 have been approved under OMB Control No. 0910–0338 (expires June 30, 2010); and 21

CFR part 814 have been approved under OMB Control No. 0910–0231 (expires November 30, 2010). Therefore, clearance by OMB under the PRA is not required.

VII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) and 25.34(e) 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. 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." Like any Federal requirement, if a State law requirement makes compliance with both Federal law and State law impossible, or would frustrate Federal objectives, the State requirement would be preempted. See *Geier* v. *American Honda Co.*, 529 U.S. 861 (2000); *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). Moreover, if a State requirement constitutes a requirement that is different from, or in addition to, a Federal requirement applicable to a medical device, and which relates to the safety or effectiveness of the device, the State law requirement is preempted. See 21 U.S.C. 360k(a), *Reigel* v. *Medtronic*, 128 S.Ct. 999 (2008). In addition to the discussion above in response to comment 7 of this document, FDA notes that, at least when a sponsor did not meet the

standard to change its labeling through a CBE supplement under this rule to include the warning a plaintiff alleges should have been added to labeling, State law liability that is premised on a failure to warn is preempted.

FDA has provided the States with an opportunity to comment on the January 2008 proposed rule. Specifically, following publication of the January 2008 proposed rule in the **Federal Register**, FDA issued a "Dear Colleague" letter on January 17, 2008. The purpose of this letter was to alert officials in various organizations within the 50 States about the rulemaking, including officials with State pharmacy boards, State medical boards, health commissioners, and drug program directors. The letter briefly explained what the rulemaking would do when it became final and it encouraged the officials to review the January 2008 proposed rule and provide FDA with any comments they may have concerning the impact this rule may have on the following: (1) On the States, (2) on the relationship between the national government and the States, or (3) on the distribution of power and responsibilities among the various levels of government. FDA received one comment that appears to be in response to this "Dear Colleague" letter. This comment is addressed in the final rule.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314, 601, and 814 are amended as follows:

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

■ 1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 2. Section 314.3 is amended in paragraph (b) by alphabetically adding the definition for "newly acquired information" to read as follows:

§ 314.3 Definitions.

* * * * *

(b) * * *

Newly acquired information means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

* * * * *

■ 3. Section 314.70 is amended by revising paragraphs (c)(6)(iii) introductory text and (c)(6)(iii)(A) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(c) * * *

(6) * * *

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

* * * * *

PART 601—LICENSING

■ 4. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 5. Section 601.12 is amended by revising paragraphs (f)(2)(i) introductory text and (f)(2)(i)(A), and by adding paragraph (f)(6) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly acquired

information, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

* * * * *

(6) For purposes of paragraph (f)(2) of this section, information will be considered newly acquired if it consists of data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

* * * * *

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

■ 6. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381.

■ 7. Section 814.3 is amended by adding paragraph (o) to read as follows:

§ 814.3 Definitions.

* * * * *

(o) *Newly acquired information* means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new

analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

■ 8. Section 814.39 is amended by revising paragraphs (d)(1) introductory text and (d)(2)(i) to read as follows:

§ 814.39 PMA supplements.

* * * * *

(d)(1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section to reflect newly acquired information that enhances the safety of the device or the safety in the use of the device may be placed into effect by the applicant prior to the receipt under § 814.17 of a written FDA order approving the PMA supplement provided that:

* * * * *

(2) * * *

(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction for which there is reasonable evidence of a causal association.

* * * * *

Dated: 8/19/08

August 19, 2008.

Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

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

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Dawn P. Hawkins