free merchandise from other merchandise in the sales or crib area.

(3) Exception to marking requirement. If the proprietor has an electronic inventory system capable of immediately identifying other merchandise from conditionally duty-free merchandise, the proprietor need not separate domestic merchandise and merchandise which was previously entered or withdrawn for consumption from conditionally duty-free merchandise or mark the merchandise.

* * * * *

PART 144—WAREHOUSE AND REWAREHOUSE ENTRIES AND WITHDRAWALS

5. The general authority citation and specific authority citation for part 144 continue to read as follows:

Authority: 19 U.S.C. 66, 1484, 1557, 1559, 1624.

* * * * *

Section 144.37 also issued under 19 U.S.C. 1555, 1562.

6. In § 144.37:

a. Paragraph (a) is amended by removing the word ''shall'' each place it appears and, in its place, adding the word ''must''; and by removing the word ''Customs'' each place it appears and, in its place, adding the term ''CBP''.

b. Paragraphs (b)(1), (f), and (h)(3) are amended by removing the word ''shall'' each place it appears and, in its place, adding the word ''must''.

c. In paragraph (b)(2), the first sentence is amended by removing the word ''shall'' and, in its place, adding the word ''must'' and by removing the reference to ''Customs'' and, in its place, adding the term ''CBP''; the second and third sentences are amended by removing the word ''shall'' each place it appears and, in its place, adding the word ''will''; and the last sentence is amended by removing the word ''shall'' and, in its place, adding the word ''must''.

d. Paragraph (d) is amended by removing the word ''Customs'' each place it appears and, in its place, adding the term ''CBP''; and by removing the word ''shall'' each place it appears and, in its place, adding the word ''must''.

e. Paragraphs (h)(2) introductory text and (h)(2)(vi) are revised to read as follows:

§ 144.37 Withdrawal for exportation.

* * * * *

(h) * * *

(2) *Sales ticket content and handling.* Sales ticket withdrawals must be made only under a blanket permit to withdrawal (see § 19.6(d) of this chapter) and the sales ticket will serve as the equivalent of the supplementary withdrawal. A sales ticket is an invoice of the proprietor's design which will include:

* * * * *

(vi) A statement on the original copy (purchaser's copy) to the effect that goods purchased in a duty-free store will be subject to duty and/or tax with personal exemption if returned to the United States. At the time of purchase, the original sales ticket must be made out in the name of the purchaser and given to the purchaser. One copy of the sales ticket must be retained by the proprietor. This copy may be maintained electronically provided the port director is satisfied that the proprietor has the ability to print the sales ticket upon the request of a CBP officer. A permit file copy will be attached to the parcel containing the purchased articles unless the proprietor has established and maintained an effective method to match the parcel containing the purchased articles with the purchaser. Additional copies may be retained by the proprietor.

* * * * *

W. Ralph Basham,

Commissioner, U.S. Customs and Border Protection.

Approved: January 10, 2008.

Timothy E. Skud,

Deputy Assistant Secretary of the Treasury.

[FR Doc. E8–522 Filed 1–15–08; 8:45 am]

BILLING CODE 9111–14–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314, 601, and 814

[Docket No. 2008N–0021]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations regarding changes to an approved new drug application (NDA), biologics license application (BLA), or medical device premarket approval application (PMA) to codify the agency's longstanding view on 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 such change. FDA is proposing to reaffirm its longstanding position that a supplemental application submitted under those provisions is appropriate to amend the labeling for an approved product only to reflect newly acquired information, as well as to clarify that such a supplemental application 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 device. The amendments proposed by this document are intended to reflect the agency's existing practices with respect to supplemental applications submitted to FDA.

DATES: Submit written or electronic comments on the amendments proposed by this document by March 17, 2008. See section VIII of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 2007M–0468 and/or RIN number __ (if a RIN number has been assigned), by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal

information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Erik Mettler, Office of Policy (HF–11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3360, FAX: 301–594–6777, e-mail: *erik.mettler@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background and Proposed Amendments

FDA is proposing to amend its regulations regarding changes to an approved NDA, BLA, or PMA to codify the agency's longstanding view on 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. With respect to drugs, FDA's current regulation, 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.[1] The corresponding regulation for biologics, 21 CFR 601.12(f)(2), provides that products with certain labeling changes may be distributed before FDA approval. Similarly, with respect to devices, 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.''[2] FDA is proposing to amend these provisions to reaffirm 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 sufficient evidence of a causal association with the drug, biologic, or medical device.

FDA is the expert public health agency charged by Congress with ensuring that drugs, biologics, and medical devices are safe and effective, and ensuring that the labeling for approved products appropriately informs users of the risks and benefits of the product. Accordingly, the Federal Food, Drug, and Cosmetic Act (the act) requires new drugs, biologics, and certain Class III medical devices to be approved by FDA prior to their distribution in interstate commerce. See 21 U.S.C. 505(a); 42 U.S.C. 262(a)(1); 21 U.S.C. 360e(a). Under these provisions, FDA's review and prior approval of both the product and its proposed labeling is a necessary condition of lawful distribution of the product in interstate commerce.

The CBE supplement procedures set forth in §§ 314.70(c)(6)(iii), 601.12(f)(2), and 814.39(d) must be understood in light of these statutory requirements. Allowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress. Indeed, permitting a sponsor to unilaterally rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated. Accordingly, FDA has issued regulations providing that, prior to a sponsor making most labeling changes, it must submit a supplemental application fully explaining the basis for the change and obtain the prior approval by FDA of the supplemental application. See §§ 314.70(b), 601.12(f)(1), 814.39(a)(2).

The CBE supplement procedures are narrow exceptions to this general rule. Although CBE supplements permit sponsors to implement labeling changes before FDA approval of the change, FDA views a CBE supplement as a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product. As with prior approval supplements, FDA will carefully review any labeling change proposed in a CBE supplement, as well as the underlying information or data supporting the change. FDA has the authority to accept, reject, or request modifications to the proposed changes as the agency deems appropriate, and has the authority to bring an enforcement action if the added information makes the labeling false or misleading. See 21 U.S.C. 352(a). For these reasons, as a practical matter, FDA encourages sponsors to consult with FDA prior to adding safety-related information to the labeling for an approved product even when such a change is submitted in a CBE supplement, and sponsors typically do so. The ultimate authority over drug, biologic, and medical device labeling, therefore, continues to rest with FDA.

The history of the CBE procedure supports this narrow understanding of these provisions. The CBE procedure can be traced to a 1965 policy that was based on FDA's enforcement discretion. In 1965, the agency stated that ''certain kinds of changes in the labeling and manufacturing of new drugs, proposed in supplemental new drug applications, should be placed into effect at the earliest possible time.'' (30 FR 993, January 30, 1965). FDA announced, therefore, that agency would ''take no action'' if a sponsor implemented certain labeling changes ''prior to his receipt of a written notice of approval of the supplemental new-drug application,'' assuming certain conditions were satisfied. (30 FR 993 at 994.)

FDA proposed what is essentially the current CBE procedure in 1982. When proposed, the agency made clear that CBE supplements were intended to apply only if the sponsor became aware of newly discovered safety information that was appropriate for inclusion in the labeling for the product. Indeed, in the preamble to the proposed rule for the CBE provision for drugs, the agency stated: ''[S]ome information, although still the subject of a supplement, would no longer require agency preclearance. These supplements would describe changes placed into effect to correct concerns about *newly discovered* risks from the use of the drug.'' (47 FR 46622, 46623, October 19, 1982) (emphasis added). In that preamble, the agency also emphasized that the CBE procedure was a limited exception to the general requirement of prior FDA approval for a labeling change:

> Although most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change, the following changes in labeling, which would make available important *new information* about the safe use of a drug product, could be made if the applicant submits a supplement when the change is

[1] CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 CFR 314.150(b)(10); *see also* 57 FR 17950, 17953, and 17961.

[2] For devices, such supplements are also referred to as Special PMA Supplements. For convenience, this document will use the term CBE supplement.

made: Changes that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdosage, or any other instruction about dosage and administration that is intended to improve the safe use of the product.

(47 FR 46622 at 46635) (emphasis added). Similarly, in the preamble to the final rule, FDA again emphasized that CBE supplements were intended as a narrow exception to the general rule that labeling changes require FDA's prior approval:

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling * * * are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately approved by FDA in advance, unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.

(50 FR 7452–01, 7470, February 22, 1985).

Recent changes to the act made by the Food and Drug Administration Amendments Act (FDAAA), Public Law 110–85, 121 Stat. 823 (September 27, 2007) confirm that Congress intends FDA to carefully regulate the content of labeling for approved products. Among other provisions, FDAAA provided new authority to FDA to initiate labeling changes for approved drugs and biologics. Under the act as amended, ''[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug,'' the agency may trigger a process to rapidly amend the labeling for the product (21 U.S.C. 355(o)(4)(A)). The FDAAA provisions were intended to ensure that FDA-initiated labeling changes would be made quickly in order to respond to new or emerging information about an approved drug or biologic. These provisions provide streamlined authority for FDA to respond to new and emerging safety information.[3] FDA believes that its understanding of §§ 314.70(c)(6)(iii) and 601.12(f)(2) as reflected in this document is consistent with this enhanced authority for FDA to control the labeling for drugs and biologics.

In the device context, FDA has previously stated that a CBE supplement constitutes ''a narrow exception to the general rule that prior FDA approval of changes to a PMA, including the labeling for a device, is a condition of lawful distribution.'' See Draft Guidance: Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process (March 9, 2007) (*http://www.fda.gov/cdrh/ode/guidance/1584.pdf*). ''Allowing a manufacturer to add a safety-related warning using a [CBE supplement] based on information that was known to the FDA during the rigorous PMA review process would undermine that important process.'' Id. For this reason, a CBE supplement may only be utilized where ''the manufacturer has newly acquired safety-related information.'' Id. Moreover, ''any such change should be considered temporary while FDA reviews the supplement, including the basis for * * * how the change enhances the safety of the device or the safety in the use of the device.'' Id.

For these reasons, FDA believes it necessary to amend its regulations to make explicit the agency's understanding that a sponsor may utilize the limited CBE provisions only to reflect *newly acquired* safety information. 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, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product. For example, if a postmarket study demonstrates that an approved product has a more severe risk of a significant adverse reaction than previously known, a CBE supplement may be appropriate. However, if a postmarket study provides data about a product that is cumulative of information previously submitted to FDA, a CBE supplement would not be appropriate. Similarly, if a sponsor receives reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, such information may be considered newly acquired information that could form the basis for an appropriate CBE supplement. However, if the reports of adverse events are consistent in type, severity, and frequency with information previously provided to FDA, such reports may not constitute newly acquired information appropriate for a CBE supplement. FDA also intends to consider significant new analyses of previously submitted data (e.g., meta-analyses) that provide novel information about the product to constitute newly acquired information. FDA invites comments regarding the circumstances when information regarding a safety issue associated with a drug, biologic, or medical device should be considered newly acquired and thus appropriate to be included in a CBE supplement.

Moreover, FDA proposes to clarify that a CBE supplement may be used only to implement labeling changes regarding contraindications,[4] warnings, precautions, or adverse reactions in circumstances when there is sufficient evidence of a causal association with the drug, biologic, or medical device.

FDA's regulations regarding the content and format of labeling for prescription drugs and biologics are codified in §§ 201.57 and 201.80 (21 CFR part 201).[5] Section 201.57(c) provides criteria for when safety information is appropriate for inclusion in the labeling for an approved drug or biologic. With respect to warnings and precautions, a sponsor is obligated to update labeling for an approved product to include ''a warning about a *clinically significant* hazard as soon as there is *reasonable evidence of a causal association* with a drug'', even though a causal relationship ''need not have been definitely established.'' (§ 201.57(c)(6) (emphasis added)). With respect to adverse reactions, the rule requires the listing of adverse reactions that are ''*reasonably associated* with use of a drug'' (§ 201.57(c)(7) (emphasis added)). The rule provides that not all adverse events observed during use of a drug are eligible for inclusion in labeling, but rather ''only those adverse events for which there is *some basis to believe there is a causal relationship* between the drug and the occurrence of the adverse event.'' Id. (emphasis added), c.f. § 314.80(e) (sponsor need not submit a 15-day alert report for an adverse drug experience obtained from a

[3] As FDA has stated, Federal law governs not only what information must appear in labeling, but also what information may not appear. (71 FR 3922 at 3935, January 24, 2006) (''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 if the additional statement is unsubstantiated or otherwise false or misleading.'')

[4] For drugs and biologics subject to the labeling requirements codified at § 201.57 (21 CFR 201.57), see also § 201.56 (21 CFR 201.56), generally contraindications cannot be substantively amended by a CBE supplement. Because all contraindications must be described in Highlights, 21 CFR 201.57(a)(9), and because Highlights cannot be amended by a CBE supplement, §§ 314.70(c)(6)(iii), 601.12(f)(2), adding or substantively amending a contraindication requires a prior approval supplement, unless FDA requests that the change be made under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(E) or the sponsor submits, and FDA approves, a waiver request under § 314.90.

[5] Section 201.57 is applicable to recently approved drugs and biologics and certain other products (see also § 201.56) (describing implementation schedule). Older products generally are subject to the labeling requirements set forth in § 201.80.

postmarketing study ''unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience''). Similarly, with respect to contraindications, § 201.57 provides that labeling should include situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit. The rule directs that sponsors list only ''[k]nown hazards and not theoretical possibilities'' as contraindications (§ 201.57(c)(5); see also 71 FR 3922 at 3927) (''FDA believes that including relative or hypothetical hazards [as contraindications] diminishes the usefulness of this section.'').

Section 201.80 sets forth similar, although not identical, criteria for the inclusion of safety-related information in the labeling for products subject to that provision. Because § 201.57 represents the agency's most recent consideration of this topic, (see 71 FR 3922), FDA proposes that, if a sponsor intends to utilize the limited CBE procedure set forth in § 314.70(c)(6)(iii) or § 601.12(f), it must possess information regarding causation sufficient to satisfy the criteria set forth in § 201.57(c), regardless of whether the drug or biologic is subject to the labeling requirements of § 201.57 or § 201.80. FDA invites comments on this topic.

Medical devices subject to PMA approval follow similar labeling standards. For example, in 1991 FDA published a memorandum describing the agency's approach to device labeling. See Device Labeling Guidance, General Program Memorandum G91–1 (March 8, 1991) (*http://www.fda.gov/cdrh/g91-1.htm*). In that guidance, the agency stated that the labeling for a medical device should include a warning ''if there is *reasonable evidence of an association* of a serious hazard with the use of the device,'' even though a causal relationship ''need not have been proved.'' Id. at section V (emphasis added). With respect to adverse reactions, the agency advised that labeling should include a listing of adverse reactions that are ''*reasonably associated* with use of a device.'' Id. at section VI (emphasis added). With respect to contraindications, the guidance recommended that labeling include situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Labeling should include only ''[k]nown hazards and not theoretical possibilities.'' Id. at section V. For example, if a hypersensitivity to an ingredient in a device has not been demonstrated, it should not be listed as a contraindication in the labeling. Id. Accordingly, FDA proposes that in order to utilize the limited CBE exception, there should be, at minimum, reasonable evidence of a causal association between the device and the warning, precaution, adverse event, or contraindication sought to be added.

Explicitly requiring that CBE supplements are utilized in a manner proposed by this amendment ensures that only scientifically justified information is provided in the labeling for an approved product. Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device or decrease the usefulness and accessibility of important information by diluting or obscuring it. As FDA has stated, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance. See, e.g., ''Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care'' (August 1993) (*http://www.fda.gov/cdrh/dsma/897.pdf*) (''Overwarning has the effect of not warning at all. The reader stops paying attention to excess warnings.'') For this reason, sponsors should seek to utilize §§ 314.70(c)(6)(iii)(A), 601(f)(2)(A), and 814.39(d)(2)(i) only in situations when there is sufficient evidence of a causal association between the drug, biologic, or medical device and the information sought to be added. For example, Draft Guidance, Public Availability of Labeling Changes in ''Changes Being Effected Supplements'' (September 2006) (*http://www.fda.gov/cder/guidance/7113dft.htm*) (''FDA would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event.''); *Colacicco* v. *Apotex Inc.*, No. 06–3107, Br. of United States (3d Cir. filed December 4, 2006) (stating that § 314.70(c)(6)(iii) ''does not alter the requirement that any warning must be based on 'reasonable evidence of an association of a serious hazard with a drug.'' (citations omitted)). Accordingly, FDA is proposing to amend §§ 314.70(c)(6)(iii)(A), 601.12(f)(2)(A), and 814.39(d)(2)(i) to make explicit the agency's view that CBE supplements may be used to strengthen a contraindication, warning, precaution, or adverse reaction only when there is sufficient evidence of a causal association.

These proposed amendments to FDA's CBE regulations are consistent with the agency's role in protecting the public health. Before approving an NDA, BLA, or PMA, the FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is scientific basis to be included in the FDA-approved labeling. Under the act, the Public Health Service Act (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. 360e(d)(2). FDA's comprehensive review 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. FDA's approval of an application is expressly conditioned upon the applicant incorporating the specified labeling changes exactly as directed. For example, §§ 314.105(b), 814.44(d)(1). Moreover, after approval, FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate. Allowing a sponsor, without prior FDA approval, to add information to the labeling for a product based solely on data previously submitted to the FDA would undermine FDA's approval process and could result in unnecessary or confusing information being placed in the labeling for a drug, biologic, or medical device.

For these reasons, FDA is proposing to amend its regulations to make explicit the agency's longstanding position and practice regarding CBE supplements. FDA does not consider this amendment to be a substantive change, and it would not alter the agency's existing practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.

II. Legal Authority

This rule, if finalized, would amend §§ 314.70, 601.12, and 814.39 in a manner consistent with the agency's current understanding and application of those provisions. 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. Both the act and the PHS Act provide FDA with authority over the labeling for approved

drugs, biologics, and medical devices, and authorizes 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,[6] 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 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.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 as amended, 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 proposed 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 the proposed amendments to existing regulations are intended only to clarify the agency's interpretation of current policy, the agency certifies that the proposed 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 proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The objective of the proposed rule is to make explicit the agency's longstanding 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 proposed rule is to codify the agency's understanding 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 sufficient evidence of a causal association with the approved product. 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 the proposed rule does not establish any new regulatory or record keeping requirements, the agency does not expect that there will be any associated compliance costs. The proposed rule simply codifies the agency's longstanding 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 the proposed codifications would promote more effective and safe use of approved products. The agency believes that any potential impacts of the proposed rule would be minimal because this action does not represent a substantive policy change.

IV. Paperwork Reduction Act of 1995

This proposed 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. 3501–3520). The collections of information in: 21 CFR part 314 have been approved under OMB Control No. 0910–0001 (expires May 31, 2008); 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, FDA tentatively concludes that the proposed requirements in this document are not subject to review by OMB because they do not constitute a ''new collection of information'' under the PRA.

V. 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.

VI. Federalism

The agency has analyzed this proposed 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.'' Under the principles of implied conflict preemption, courts

[6] 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)).

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).

If finalized as proposed, this rule codifies longstanding agency policy and understanding with respect to §§ 314.70(c)(6)(iii), 601.12(f) and 814.39(d). To the extent that state law would require a sponsor to add information to the labeling for an approved drug or biologic without advance FDA approval based on information or data as to risks that are similar in type or severity to those previously submitted to the FDA, or based on information or data that does not provide sufficient evidence of a causal association with the product, such a state requirement would conflict with federal law. In such a situation, it would be impossible to market a product in compliance with both federal and state law, and the state law would ''stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,'' *Hines*, 312 U.S. at 67. Moreover, such a state law requirement relating to a medical device would constitute a requirement that is different from, or in addition to, a federal requirement applicable to the device, and which relates to the safety or effectiveness of the device. 21 U.S.C. 360k(a).

FDA believes that the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that when adjudication or rulemaking could have a preemptive effect on state law, ''the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.'' By publication of this proposed rule, FDA invites comments from State and local officials. FDA also intends to provide separate notice of this proposed rule to the States.

VII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or three paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that in January 2008, the FDA Web site is expected to transition to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. After the transition date, electronic submissions will be accepted by FDA through the FDMS only. When the exact date of the transition to FDMS is known, FDA will publish a **Federal Register** notice announcing that date.

VIII. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal be effective on the date of its publication in the **Federal Register**.

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.

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, it is proposed that 21 CFR parts 314, 601, and 814 be 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 of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (e.g., meta-analyses).

* * * * *

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;

* * * * *

(5) 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 of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (*e.g.*, meta-analyses).

* * * * *

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 of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (*e.g.*, meta-analyses).

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: December 4, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E8–702 Filed 1–15–08; 8:45 am]

BILLING CODE 4160–01–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 704, 720, 721, and 723

[EPA–HQ–OPPT–2007–0392; FRL–8131–8]

RIN 2070–AJ21

Proposed Clarification for Chemical Identification Describing Activated Phosphors for TSCA Inventory Purposes

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed clarification.

SUMMARY: This document proposes a clarification under which activated phosphors that are not on the Toxic Substances Control Act (TSCA) section 8(b) Chemical Substance Inventory (TSCA Inventory) would be considered to be new chemical substances under TSCA section 5, thus would be subject to the notification requirements under TSCA section 5(a) new chemical notification requirements. In certain letters and other interpretations issued by EPA from 1978 to 2003, it appears that the Agency erroneously indicated that activated phosphors constitute solid mixtures for purposes of the TSCA Inventory, and thus that they were not separately reportable as chemical substances under TSCA section 5(a) new chemical notification requirements. This proposed clarification is necessary because EPA's interpretations in this area have not been consistent. Given this past inconsistency, EPA is seeking comment on its proposed clarfication.

DATES: Comments must be received on or before March 17, 2008.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPPT–2007–0392, by one of the following methods:

• *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

• *Mail*: Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.

• *Hand Delivery*: OPPT Document Control Office (DCO), EPA East Bldg., Rm. 6428, 1201 Constitution Ave., NW., Washington, DC. Attention: Docket ID Number EPA–HQ–OPPT–2007–0392. The DCO is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the DCO is (202) 564–8930. Such deliveries are only accepted during the DCO's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to docket ID number EPA–HQ–OPPT–2007–0392. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov website is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses. For additional information about EPA's public docket, visit the EPA Docket Center homepage at *http://www.epa.gov/epahome/dockets.htm*.

Docket: All documents in the docket are listed in the docket index available in regulations.gov. To access the electronic docket, go to *http://www.regulations.gov*, select ''Advanced Search,'' then ''Docket Search.'' Insert the docket ID number where indicated and select the ''Submit'' button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket