

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. FDA-2013-N-0500]

RIN 0910-AG94

Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to revise and clarify procedures for application holders of an approved drug or biological product to change the product labeling to reflect certain types of newly acquired information in advance of FDA's review of the change. The proposed rule would create parity among application holders with respect to such labeling changes by permitting holders of abbreviated new drug applications (ANDAs) to distribute revised product labeling that differs in certain respects, on a temporary basis, from the labeling of its reference listed drug (RLD) upon submission to FDA of a "changes being effected" (CBE-0) supplement. The proposed rule describes the process by which information regarding a CBE-0 labeling supplement submitted by a new drug application (NDA) holder, an ANDA holder, or a biologics license application (BLA) holder would be made publicly available during FDA's review of the labeling change and clarifies requirements for all ANDA holders to submit conforming labeling revisions after FDA has taken an action on the NDA or ANDA holder's CBE-0 labeling supplement. The proposed

rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the "Highlights of Prescribing Information" for drug products with labeling in the "Physician Labeling Rule" (PLR) format.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section VII for the proposed effective date of a final rule based on this proposed rule. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], (see the "Paperwork Reduction Act of 1995" section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-0500 and/or Regulatory Information Number (RIN) 0910-AG94, by any of the following methods, except that comments on information collection issues under the PRA must be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) (see the "Paperwork Reduction Act of 1995" section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-0500 and RIN 0910-AG94 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the SUPPLEMENTARY INFORMATION section.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> 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: Janice L. Weiner, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6304, Silver Spring, MD 20993-0002, 301-796-3601.

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Executive Summary

Purpose of the Regulatory Action

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 301 et seq.) and the Public Health Service Act (the PHS Act) (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. FDA is proposing to amend its regulations to revise and clarify procedures for application holders to change the labeling of an approved drug or biological product to reflect certain types of newly acquired information in advance of FDA's review of the change through a CBE-0 supplement. The proposed rule would create parity among application holders with respect to these safety-related labeling changes by permitting ANDA holders to distribute revised

generic drug labeling that differs in certain respects, on a temporary basis, from the RLD labeling upon submission to FDA of a CBE-0 supplement.

Summary of the Major Provisions of the Regulatory Action

The proposed rule would enable ANDA holders to update product labeling promptly to reflect certain types of newly acquired information related to drug safety, irrespective of whether the revised labeling differs from that of the RLD. An ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the RLD at the same time that the supplement to the ANDA is submitted to FDA, unless approval of the NDA has been withdrawn. This proposal would ensure that the NDA holder for the RLD is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

If approval of the NDA for the RLD has been withdrawn (for reasons other than safety or effectiveness), FDA's evaluation of the labeling change proposed by the ANDA holder would consider any submissions related to the proposed labeling change from any other application holder for drug products containing the same active ingredient.

To make the safety-related changes to drug labeling described in a CBE-0 supplement readily available to prescribing health care providers and the public while FDA is reviewing the supplement, FDA proposes to establish a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement.

A supplement to an approved ANDA for a safety-related labeling change that is submitted in a prior approval supplement or in a CBE-0 supplement would be approved upon

approval of the same labeling change for the RLD. The proposed rule would establish a 30-day timeframe in which all ANDA holders would be required to submit a CBE-0 supplement with conforming labeling changes after FDA approval of a revision to the labeling for the RLD.

The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the "Highlights of Prescribing Information" for drug products with labeling in the PLR format. This is intended to remove an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications) for drug products with labeling in the PLR format.

Finally, FDA regulations provide that FDA may take steps to withdraw approval of an ANDA if the generic drug labeling is no longer consistent with the labeling for the RLD, subject to certain exceptions specified in the regulations. The proposed rule would amend the regulations to add a new exception for generic drug labeling that is temporarily inconsistent with the labeling for the RLD due to safety-related labeling changes submitted by the ANDA holder in a CBE-0 supplement.

Costs and Benefits

The economic benefits to the public health from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing health care providers and the public could be improved. The primary estimate of the costs of the proposed rule includes costs to ANDA and NDA holders for submitting and reviewing CBE-0 supplements. The Agency estimates the net annual social costs to be between \$4,237 and \$25,852. The present discounted value over 20 years would be in the

range of \$63,040 to \$384,616 at a 3 percent discount rate, and in the range of \$44,890 to \$273,879 at a 7 percent discount rate.

I. Background

A. Drug Labeling

Under the FD&C Act, the PHS Act, and FDA regulations, the Agency makes decisions regarding the approval of marketing applications, including supplemental applications, based on a comprehensive analysis of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see 21 U.S.C. 355(d); 42 U.S.C. 262).

FDA-approved drug labeling summarizes the essential information needed for the safe and effective use of the drug,¹ and reflects FDA's finding regarding the safety and effectiveness of the drug under the labeled conditions of use. The primary purpose of labeling (commonly referred to as the "package insert" or "prescribing information") for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug labeling is directed to health care practitioners, but may include FDA-approved patient labeling (see § 201.57(c)(18) (21 CFR 201.57(c)(18)) and 21 CFR 201.80(f)(2)). The over-the-counter (OTC) Drug Facts labeling is directed to consumers and conveys information in a clear, standardized format to enable patient self-selection of an appropriate drug and enhance the safe and effective use of the drug (see 21 CFR 201.66).

¹ For the purposes of this document, unless otherwise specified, references to "drugs" or "drug products" include drugs approved under the FD&C Act and biological products licensed under the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

All drugs have risks, and health care practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used more widely or under diverse conditions, new information regarding the risks and benefits of a drug may become available. This may include new risks or new information about known risks. Accordingly, all holders of NDAs, ANDAs, and BLAs are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA (see §§ 314.80(b), 314.98(a), and 600.80(b) (21 CFR 314.80(b), 314.98(a), and 600.80(b))). Application holders must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and comply with applicable reporting and recordkeeping requirements (see §§ 314.80(b), 314.98(a), and 600.80(b))). Application holders also must comply with requirements for other postmarketing reports under § 314.81 (21 CFR 314.81) and 21 CFR 600.81 and section 505(k) of the FD&C Act (21 U.S.C. 355(k)). These requirements include submission of an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling (see § 314.81).

When new information becomes available that causes information in labeling to be inaccurate, the application holder must take steps to change the content of its labeling, in accordance with §§ 314.70, 314.97, and 601.12 (21 CFR 314.70, 314.97, and 601.12). All

holders of marketing applications for drug products have an ongoing obligation to ensure their labeling is accurate and up-to-date. A drug is misbranded in violation of the FD&C Act when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings (see 21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)).

B. Current Requirements Related to Changes to Approved Drug Labeling

For most substantive changes to product labeling, an application holder is required to submit a prior approval supplement and receive FDA approval for the change (see §§ 314.70(b) and 601.12(f)(1)). However, in the interest of public health, the regulations permit certain labeling changes based on newly acquired information about an approved drug to be implemented upon receipt by the Agency of a supplemental application that includes the change. These supplements are commonly referred to as "changes being effected supplements" or "CBE-0 supplements" (see §§ 314.70(c)(6)(iii) and 601.12(f)(2)).

The current regulations provide that application holders may submit CBE-0 supplements for the following types of changes to product labeling:

- 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);
- To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose;
- To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
- To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

- Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

The CBE-0 supplement procedures originated from a 1965 policy based on FDA's enforcement discretion regarding certain labeling changes that should be placed into effect "at the earliest possible time" (see "Supplemental New-Drug Applications," 30 FR 993, January 30, 1965). Over the years, FDA has clarified the types of labeling changes that may be made by a CBE-0 supplement through a series of rulemakings.

In 1985, FDA updated its procedures for CBE-0 supplements and emphasized that CBE-0 supplements were intended as a narrow exception to the general rule that labeling changes require FDA's prior approval (see "New Drug and Antibiotic Regulations"; final rule, 50 FR 7452 at 7470, February 22, 1985).

In 2006, FDA amended its regulations governing the content and format of prescription drug labeling to require, among other things, that the labeling of new and recently approved products include introductory prescribing information titled "Highlights of Prescribing Information" (see 21 CFR 201.57(a); see also "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products"; final rule, 71 FR 3922, January 24, 2006). The "Highlights of Prescribing Information" (Highlights) is intended to summarize the information that is most important for prescribing the drug safely and effectively, and to organize the information into logical groups to enhance accessibility, retention, and access to the more detailed information (see 71 FR 3922 at 3931). As part of this rulemaking, FDA amended the CBE-0 labeling supplement provisions to exclude most changes to the information required in the Highlights, which must be made by a prior approval supplement unless FDA specifically

requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request under § 314.90 (21 CFR 314.90).

In 2008, FDA amended the regulations governing CBE-0 supplements to codify the Agency's view that a CBE-0 labeling supplement is appropriate only to reflect newly acquired information and to clarify that a CBE-0 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 explained that these requirements are intended to help ensure that scientifically accurate information appears in the approved labeling for such products ("Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices"; final rule, 73 FR 49603 at 49604, August 22, 2008).

FDA carefully reviews any labeling change proposed in a CBE-0 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)). If the newly acquired information changes the benefit/risk balance for the drug, such that the product no longer meets FDA's standard for approval, then FDA will take appropriate action (see 21 U.S.C. 355(e) and 355-1).

The CBE-0 supplement regulations allow application holders to comply with the requirement to update labeling promptly 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 other risk information as required by the regulations (§§ 201.57(c) and 201.100(d)(3)).

C. Specific Labeling Requirements Related to Generic Drugs

The FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: An NDA containing full reports of investigations of safety and effectiveness, for which the requirements are set out in section 505(b) and (c) of the FD&C Act, and an ANDA, for which the requirements are set out in section 505(j).

The ANDA category can be further subdivided into an ANDA and a "petitioned ANDA." An ANDA must contain information to show that the proposed drug product is the same as a drug previously approved under section 505(c) of the FD&C Act (the RLD) with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD. An applicant that can meet the requirements under section 505(j) of the FD&C Act for approval may rely upon the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of an NDA submitted under section 505(b)(1) of the FD&C Act. A "petitioned ANDA" is a type of ANDA for a drug that differs from a previously approved drug product in dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient), for which FDA has determined, in response to a suitability petition submitted under section 505(j)(2)(C) of the FD&C Act, that clinical studies are not necessary to demonstrate safety and effectiveness.

A generic drug is classified as therapeutically equivalent to the RLD if it is a pharmaceutical equivalent and has demonstrated bioequivalence (see "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book), 33rd ed., 2013, p. vii). The generic drug program is based on the principle that "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce

the same clinical effect and safety profile as the prescribed product" (Orange Book, 33rd ed., 2013, p. vii). Currently, approximately 80 percent of all drugs dispensed are generic drugs (Ref. 1). After the introduction of a generic drug, the market share of the "brand name" drug (i.e., the drug approved in an NDA under section 505(c) of the FD&C Act) may drop substantially. Among drugs for which a generic version is available, approximately 94 percent are dispensed as a generic (Ref. 1). For any given brand name drug, there may be multiple approved generic drugs, and the prescribing health care provider ordinarily would not know which generic drug may be substituted for the prescribed product under applicable State law.

A generic drug is required to have the same labeling as the RLD at the time of approval, except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93) or because the drug product and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act). FDA has described those differences in § 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) as including, for example, differences in formulation, bioavailability, or pharmacokinetics; labeling revisions made to comply with current FDA labeling guidelines or other guidance; or omission of an indication or other aspect of labeling protected by patent or exclusivity. FDA has generally taken the position that a generic drug must maintain the same labeling as the RLD throughout the lifecycle of the generic drug product (see § 314.150(b)(10) (21 CFR 314.150(b)(10))). Thus, if an ANDA holder believes that newly acquired safety information should be added to its product labeling, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic drug(s) and the RLD should be revised (see 57 FR 17950 at 17961; April 28, 1992).

Although FDA has expressed differing views on this issue over the years, FDA generally has advised that an ANDA holder may use the CBE-0 supplement process only to update its product labeling to conform with approved labeling for the RLD or to respond to FDA's specific request to submit a labeling change under this provision, and may not unilaterally change ANDA labeling in a manner that differs from the RLD (see § 314.150(b)(10); see also 57 FR 17950 at 17961, and "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices"; proposed rule, 73 FR 2848 at 2849; footnote 1; January 16, 2008).

At the time of FDA's adoption of the generic drug regulations in 1992, FDA believed it was important that product labeling for the RLD and any generic drugs be the same to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. However, as the generic drug industry has matured and captured an increasing share of the market, tension has grown between the requirement that a generic drug have the same labeling as its RLD, which facilitates substitution of a generic drug for the prescribed product, and the need for an ANDA holder to be able to independently update its labeling as part of its independent responsibility to ensure that the labeling is accurate and up-to-date. In the current marketplace, in which approximately 80 percent of drugs dispensed are generic and, as we have learned, brand name drug manufacturers may discontinue marketing after generic drug entry, FDA believes it is time to provide ANDA holders with the means to update product labeling to reflect data obtained through postmarketing surveillance, even though this will result in temporary labeling differences among products. In a study of FDA safety-related drug labeling changes made in 2010, FDA found that the median time from initial approval of the drug product to the time of making the safety-related labeling change was 11 years, which confirms that data supporting

labeling changes may become available after approval of generic versions of the drug product (see Ref. 2). FDA found that "[t]he most critical safety-related label changes, boxed warnings and contraindications, occurred a median 10 and 13 years after drug approval (and the range spanned from 2 to 63 years after approval), underscoring the importance of persistent and vigilant postmarket drug safety surveillance" (Ref. 2).

D. Recent Court Decisions

In two recent cases, the United States Supreme Court considered the issue of whether Federal law preempts State law tort claims against pharmaceutical manufacturers for failing to provide adequate warnings in drug product labeling ("failure-to-warn claims") (see Pliva, Inc. v. Mensing, 131 S.Ct. 2567 (2011) and Wyeth v. Levine, 555 U.S. 555 (2009)). In Pliva v. Mensing, the Court held that the difference between NDA and ANDA holders' ability to independently change product labeling through CBE-0 supplements leads to different outcomes on whether Federal labeling requirements preempt State law failure-to-warn claims. In Wyeth v. Levine, the Court decided that Federal law does not preempt a State law failure-to-warn claim that a brand name drug's labeling did not contain an adequate warning. The Court found that the drug manufacturer could have unilaterally added a stronger warning to product labeling under the CBE-0 regulation as applied to NDAs, and absent clear evidence that FDA would not have approved such a labeling change, it was not impossible for the manufacturer to comply with both Federal and State requirements. The Court reaffirmed that "through many amendments to the [FD&C Act] and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times" (555 U.S. at 570-571).

Two years later, in Pliva v. Mensing, the Court decided that Federal law does preempt a State law failure-to-warn claim that a generic drug's labeling did not contain an adequate warning. The Court deferred to FDA's interpretation of its CBE-0 supplement and labeling regulations for ANDAs, and found that Federal law did not permit a generic drug manufacturer to use the CBE-0 supplement process to unilaterally strengthen warnings in its labeling or to issue additional warnings through "Dear Health Care Professional" letters, which FDA "argues...qualify as 'labeling' " (131 S.Ct. at 2576). The Court found that, under the current regulatory scheme, it was impossible for a generic drug manufacturer to comply with its Federal law duty to have the same labeling as the RLD and satisfy its State law duty to provide adequate labeling (131 S.Ct. at 2578). In September 2011, Public Citizen petitioned the Agency to revise its regulations in response to the Mensing decision (see Docket No. FDA-2011-P-0675).

As a result of the decisions in Wyeth v. Levine and Pliva v. Mensing, an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and thus access to the courts is dependent on whether an individual is dispensed a brand name or generic drug. The Mensing decision alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date.

We are proposing to change our regulations to expressly provide that ANDA holders may distribute revised labeling that differs from the RLD upon submission of a CBE-0 supplement to FDA. FDA's proposed revisions to its regulations would create parity between NDA holders and ANDA holders with respect to submission of CBE-0 supplements for safety-related labeling changes based on newly acquired information. This proposal is also intended to ensure that

generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements. If this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs.

II. Description of the Proposed Rule

A. Supplement Submission for Safety-Related Labeling "Changes Being Effectuated" (Proposed §§ 314.70(b)(2), (c)(6), and (c)(8) and 601.12(f)(2))

1. Equal Applicability to NDA Holders and ANDA Holders (Proposed § 314.70(c)(8))

We are proposing to add § 314.70(c)(8) to enable ANDA holders to submit a CBE-0 supplement for generic drug labeling that differs from the labeling of the RLD and to establish that § 314.70(c)(6)(iii) applies equally to the holder of an approved NDA or ANDA. Proposed § 314.70(c)(8) states that an application holder may submit to its approved NDA or ANDA a supplement described by § 314.70(c)(6)(iii).

If an NDA holder or ANDA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(D), the NDA holder or ANDA holder must submit a CBE-0 supplement (see § 314.70(c)(6)(iii); see also 21 CFR 314.3(b) (defining "newly acquired information")). As discussed in section I.A, all application holders, including ANDA holders, are required to conduct surveillance, evaluation, and reporting of postmarketing adverse drug experiences and, if warranted, to propose revisions to product labeling. Proposed § 314.70(c)(8) would expressly permit ANDA holders to update product labeling promptly to reflect newly acquired information that meets the criteria described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(D) irrespective of whether the revised labeling differs

from that of the RLD. In addition, if an ANDA holder submits a CBE-0 supplement for a labeling change that meets the criteria described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(E), the ANDA holder may distribute a "Dear Health Care Provider" letter (which also meets the statutory definition of "labeling") regarding this labeling change in the same manner as an NDA holder or BLA holder, and be subject to the same statutory prohibition against marketing a misbranded product (see 21 U.S.C. 321(m), 331(a) and (b), and 352, and 21 CFR 201.100(d)(1) and 202.1(l)(2)). A "Dear Health Care Provider" letter may be used to disseminate the important new drug safety information that warranted the CBE-0 supplement, for example, a significant hazard to health or other important change in product labeling (see 21 CFR 200.5). FDA will continue to undertake any communication plans to health care providers (including distribution of "Dear Health Care Provider" letters) that are part of Risk Evaluation and Mitigation Strategies (REMS) that include one or more generic drugs (see 21 U.S.C. 355-1(i)(2)).

The obligation to ensure that labeling is accurate and up-to-date applies equally to all ANDA holders. In certain circumstances, if the RLD approved under section 505(c) of the FD&C Act has been withdrawn from the market, FDA may select a drug product approved in an ANDA (including a petitioned ANDA) to be the "reference standard" that an applicant seeking approval of an ANDA that relies upon the withdrawn RLD must use in conducting an in vivo bioequivalence study required for approval (see 57 FR 17950 at 17954). However, the duty to maintain accurate product labeling does not differ between an ANDA designated as the reference standard for bioequivalence studies and other approved ANDAs.

FDA acknowledges that there may be concerns about temporary differences in safety-related labeling for drugs that FDA has determined to be therapeutically equivalent, especially if multiple ANDA holders submit CBE-0 supplements with labeling changes that differ from each

other and from the RLD. FDA also recognizes that health care practitioners are unlikely to review product labeling for each of the generic drugs that may be substituted for the prescribed product when making treatment decisions with their patients based on the balance of potential benefits and risks of the drug product for that patient. To address these concerns, FDA proposes to establish a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement while FDA is reviewing the supplement (see proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii)). The public may subscribe to FDA's free email subscription service to receive an email message each time there is an update to this proposed FDA Web page.

The FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: The active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement). It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the NDA holder for the RLD, as well as other ANDA holders. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page

through a link to FDA's online labeling repository at <http://labels.fda.gov>. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at <http://labels.fda.gov>. As discussed in section II.B, a prior approval supplement or CBE-0 supplement submitted by an ANDA holder will be approved upon the approval of the same safety-related labeling change for the RLD approved in an NDA under section 505(c) of the FD&C Act, except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's prior approval supplement or CBE-0 supplement (see section 505(j)(2)(A)(v) of the FD&C Act and proposed § 314.97(b); see also section II.A.1.b and d). Upon FDA approval of revised labeling, other ANDA holders will be required to submit a CBE-0 supplement with conforming revisions. We invite comment on this approach.

Proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii) state that FDA will promptly post on its Web site information regarding labeling changes proposed in a CBE-0 supplement to an NDA, ANDA, or BLA. This proposal is intended to enhance transparency and facilitate access by health care providers and the public to labeling containing newly acquired information about important drug safety issues so that such information may be used to inform treatment decisions. We also invite comment on whether the benefits of a dedicated FDA Web page for CBE-0 supplements could be realized through modification of FDA's existing online labeling repository (<http://labels.fda.gov>). For example, the online labeling repository could be modified to enable a separate listing of pending CBE-0 supplements, thereby improving existing resources and consolidating labeling information on a single FDA Web page.

Current §§ 314.70(c)(6) and 601.12(f)(2) state that the application holder may distribute the drug accompanied by the revised labeling upon submission to FDA of a CBE-0 supplement. However, FDA expects that if an application holder acquires important new safety-related information that warrants submission of a CBE-0 supplement under §§ 314.70(c)(6) or 601.12(f)(2), the application holder will use available means (e.g., distribution of revised labeling in electronic format to the public) to distribute the revised labeling at the time of submission of the CBE-0 supplement to FDA (compare section II.A.1.d). Indeed, the need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for this exception to the general requirement for FDA approval of revised labeling prior to distribution (see section I.B). Accordingly, we are proposing to expressly require that applicants submit final printed labeling in structured product labeling (SPL) format at the time of submission of the CBE-0 supplement so that the revised labeling can be made publicly available on FDA's Web site and in other databases (e.g., DailyMed, a Web site provided by the National Library of Medicine that includes drug labeling submitted to FDA) promptly after submission. This proposed change would make the regulations consistent with FDA's previous announcement that "the Agency will make the revised labeling proposed in a CBE supplement publicly available on its Web site and through the DailyMed shortly after the CBE supplement is received and before FDA has necessarily reviewed or approved it" (draft guidance for industry on "Public Availability of Labeling Changes in 'Changes Being Effectuated' Supplements" (2006)).² We note that the technical means by which the CBE-0 supplements are

² When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

made publicly available through the FDA Web site may change with evolving technology and Agency practices.

Proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii) would require the applicant to verify that the correct information regarding the labeling changes proposed in its CBE-0 supplement appears on FDA's Web page. If the information is incorrect, then the applicant must contact FDA within 5 business days of posting on the FDA Web page. The applicant may determine that information regarding the labeling changes proposed in its CBE-0 supplement has been posted on the FDA Web page by monitoring the FDA Web page after submission of a CBE-0 supplement or subscribing to FDA's Web page to receive an email notification. FDA intends to identify the FDA contact person(s) who should receive any corrections to such information for NDAs, ANDAs, and BLAs on the proposed FDA Web page. We invite comment on whether this is a sufficient amount of time for an applicant to check the accuracy and completeness of the posted information regarding the CBE-0 supplement and the link to current labeling.

a. Contents of supplement. We are proposing to add § 314.70(c)(8)(i) to clarify FDA's expectations regarding the contents of a CBE-0 supplement submitted under § 314.70(c)(6)(iii), and to facilitate publication of information regarding the CBE-0 supplement on FDA's Web page. Current § 314.70(c)(4) requires that a CBE supplement include information listed in § 314.70(b)(3)(i) through (b)(3)(vii), which describes information that must be included in a CBE supplement for a manufacturing change. To clarify FDA's expectations for the contents of a CBE-0 labeling supplement and to facilitate listing information on FDA's proposed Web page, we are proposing to require that a CBE-0 supplement submitted under § 314.70(c)(6)(iii) contain the following information:

i. The application number(s) of the drug product(s) involved. If a CBE-0 supplement is being submitted by an NDA or ANDA holder to multiple applications for a drug product or product class, the application holder should identify the application number of each application to which the CBE-0 supplement is being submitted.

ii. A description of the labeling change proposed in the CBE-0 supplement. The applicant should submit a proposed narrative description of the proposed labeling change in the CBE-0 supplement for posting on the FDA Web page. This brief narrative description should include the affected section(s) of labeling, the labeling change, and the source of the data (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study). For example, "Revised contraindication: Drug X is contraindicated in patients with diabetes. Source: Published literature, epidemiologic study."

iii. The basis for the labeling change proposed in the CBE-0 supplement. The basis for the labeling change proposed in the CBE-0 supplement should include available data supporting the change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study). If the supplement has been submitted in response to FDA's specific request to submit a CBE-0 supplement for the labeling change (see § 314.70(c)(6)(iii)(E)), the applicant should describe the specific change requested by FDA and reference the FDA communication containing the request.

iv. A copy of the product labeling proposed in the CBE-0 supplement. A copy of the final printed labeling containing the changes being effected should be provided in SPL format for posting on FDA's Web site and distribution to DailyMed. The application holder also should submit a copy of the current product labeling annotated with the labeling change proposed in the CBE-0 supplement (e.g., use of underscoring and/or strikethrough text to show the changes being

effected in the product labeling proposed in the CBE-0 supplement as compared to the approved labeling).

v. Confirmation that notice has been sent to the NDA holder for the RLD. If the changes being effected supplement is submitted by an ANDA holder and approval of the NDA for the RLD has not been withdrawn under § 314.150, the ANDA holder must include in its submission a statement confirming that the notice described in proposed § 314.70(c)(8)(ii) has been sent to the NDA holder for the RLD.

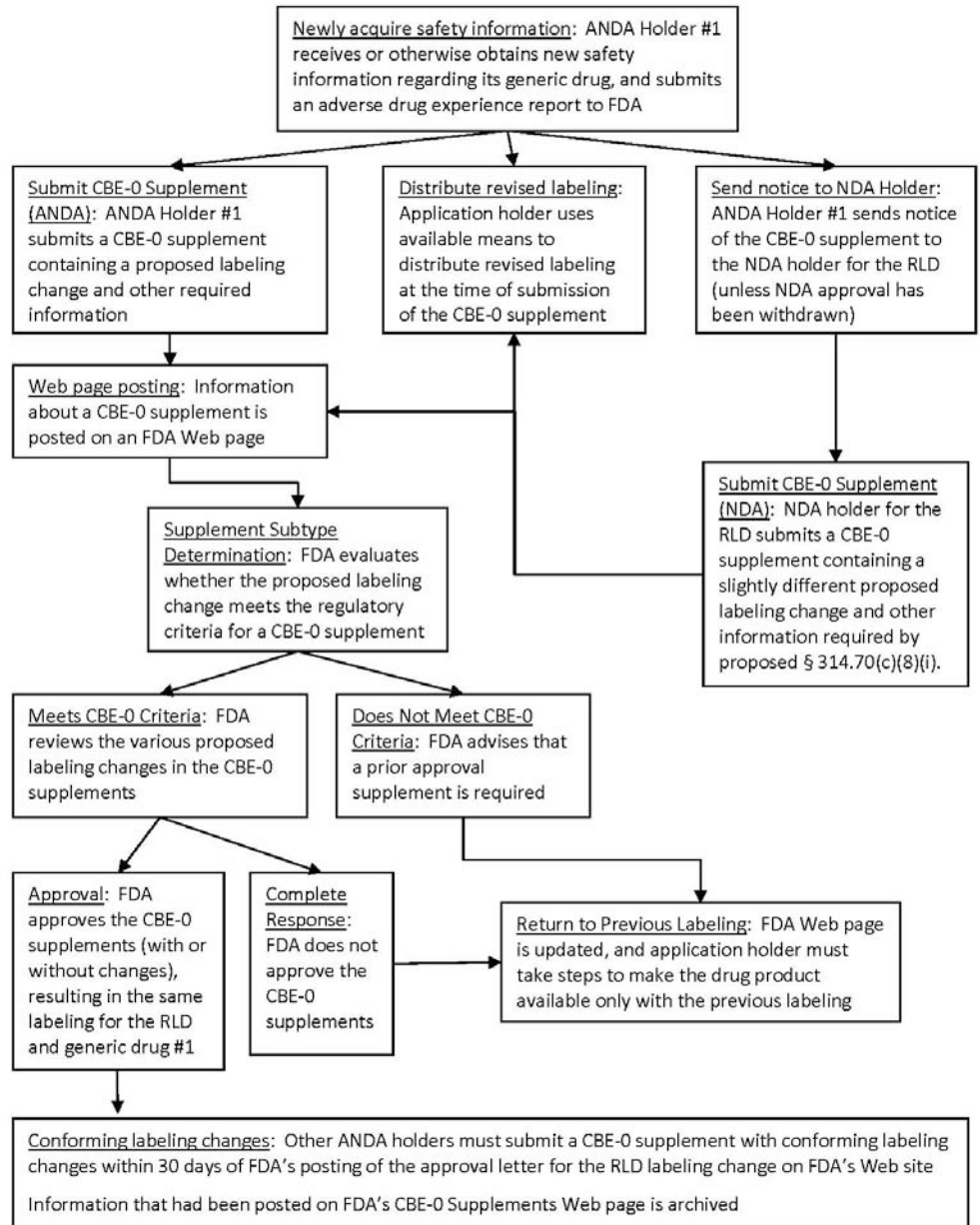
b. Notice of labeling changes being effected. We are proposing to add § 314.70(c)(8)(ii) to require an ANDA holder to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change (with any personally identifiable information redacted), to the NDA holder for the RLD at the same time that the supplement to the ANDA is submitted to FDA, unless approval of the NDA has been withdrawn under § 314.150. This proposal would ensure that the NDA holder for the RLD is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

The ANDA holder would be required to send a copy of the information (e.g., published literature, spontaneous adverse event reports) supporting the labeling change described in the CBE-0 supplement to the NDA holder for the RLD so that the NDA holder may consider this information as part of its review and evaluation of postmarketing data under § 314.80(b). If the information supporting the ANDA holder's labeling change described in the CBE-0 supplement contains personally identifiable information (e.g., spontaneous adverse event reports), the ANDA holder should redact that information prior to sending a copy of the information to the NDA holder for the RLD, in accordance with 21 CFR 20.63(f). The NDA holder has full access to the

data upon which the RLD was approved and, in most cases, has substantial knowledge about the postmarketing experience for the drug product. FDA's analysis of whether the labeling change proposed by an ANDA holder in a CBE-0 supplement should be approved (and required for inclusion in the labeling of all versions of the drug) would benefit from the views of the NDA holder for the listed drug that was the basis for ANDA submission. Other holders of NDAs or ANDAs for drug products containing the same active ingredient may learn of pending CBE-0 supplements by subscribing to FDA's proposed Web page, and also may submit CBE-0 supplements or provide comments to FDA regarding a pending CBE-0 supplement. This approach to considering information from other application holders is intended to mitigate concerns that a single ANDA holder may not possess sufficient data to perform an adequate assessment of the potential new safety concern raised by the newly acquired information.

It should be emphasized that interpretation of postmarketing safety data is complex, involving analysis of postapproval clinical data, detailed review of adverse drug experience reports in the context of relevant clinical studies, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information. FDA recognizes that decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree, and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information (see Guidance on "Drug Safety Information--FDA's Communication to the Public" (2007)). Figure 1 illustrates one of the possible scenarios involving submission of CBE-0 supplements by multiple application holders.

Figure 1. Example of Process for Submission of CBE-0 Supplements by ANDA Holder and NDA Holder



Proposed § 314.70(c)(8)(ii) would provide that an NDA holder or any ANDA holder may submit (on its own initiative or in response to a request from FDA) a labeling supplement or correspondence to its NDA or ANDA, as applicable, regarding the labeling changes proposed in a CBE-0 supplement. It is expected that a valid safety concern regarding a generic drug product also would generally warrant a change to the labeling through a CBE-0 supplement by the NDA holder for the RLD and, as a consequence, other generic drug products that reference the RLD. In the event that the NDA holder for the RLD does not submit a supplement seeking approval for a related or conforming labeling change, FDA may send a supplement request letter to the NDA holder or, if appropriate, notify the responsible person of new safety information under section 505(o)(4) of the FD&C Act (see 21 U.S.C. 355(o)(2)(A) defining "responsible person"). In situations in which the safety information prompting the submission of the CBE-0 supplement would require a label change for other drugs containing the same active ingredient, even if approved under a different NDA, FDA also may send a supplement request letter to the persons responsible for those other drugs.

We recognize that the authority to order safety labeling changes under section 505(o)(4) of the FD&C Act for new safety information about a risk of a serious adverse drug experience will not apply to all potential safety-related labeling changes (see 21 U.S.C. 355-1(b) defining "new safety information" and "serious adverse drug experience"). Based on our experience, we expect that NDA holders will implement safety-related labeling changes requested by FDA even if not required under section 505(o)(4) of the FD&C Act. In circumstances in which section 505(o)(4) of the FD&C Act does not apply, if the NDA holder declined to submit a supplement to make the change that FDA has concluded is appropriate, FDA would consider whether the

NDA holder's failure to update its labeling would warrant the initiation of proceedings to withdraw approval of the NDA (see section 505(e) of the FD&C Act).

It should be noted that if an NDA holder has discontinued marketing a drug product, but approval of the NDA has not been withdrawn under § 314.150, the NDA holder still must comply with applicable statutory and regulatory requirements. These requirements include, for example, postmarketing reporting of adverse drug experiences, submission of an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling. If approval of the NDA for the RLD is withdrawn under § 314.150 for reasons other than safety or effectiveness, any generic versions that remain on the market will be expected to contain the same essential labeling.

c. Distribution of revised labeling. We are proposing to add § 314.70(c)(8)(iii) and revise § 601.12(f)(2)(ii) to expressly describe our longstanding practice with respect to labeling supplements that have been submitted as CBE-0 supplements, but that do not meet the regulatory criteria for CBE-0 supplements, and thus do not fall within this narrow exception to the general requirement for FDA approval of revised labeling prior to distribution. Proposed §§ 314.70(c)(8)(iii) and 601.12(f)(2)(ii) explain that if FDA determines during its review period that the supplement does not meet the criteria described in § 314.70(c)(6)(iii) or § 601.12(f)(2)(i), as applicable, the supplement will be converted to a prior approval supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling. In this scenario, the manufacturer must take steps to make the drug product available only with the previous version of the label. This may include, for example, replacing the CBE-0

labeling with the previous labeling on the manufacturer's Web site, requesting replacement of the CBE-0 labeling with the previous labeling on <http://labels.fda.gov>, and attaching the previous package insert to the drug product as soon as feasible thereafter or at the time of next printing of the product labeling for packaging.

This approach is consistent with our clarifying revision in proposed § 314.70(c)(7), which explains that if the Agency does not approve the supplemental application, the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling. The current text of § 314.70(c)(7) describes the implications of a complete response letter to the applicant for a CBE supplement for manufacturing changes, and does not expressly address CBE-0 labeling supplements. For consistency with § 314.110 (21 CFR 314.110), we are proposing to replace the word "disapproves" in § 314.70(c)(7) with the phrase "issues a complete response letter" and to make other editorial changes for clarity.

d. Conforming labeling requirements. Proposed § 314.70(c)(8)(iv) would establish a 30-day timeframe in which ANDA holders are required to submit a CBE-0 supplement under § 314.70(c)(6)(iii)(E) with conforming labeling after FDA approval of a revision to the labeling for the RLD. Currently, FDA advises ANDA holders to revise product labeling to conform to the labeling of the RLD "at the very earliest time possible" (see guidance for industry on "Revising ANDA Labeling Following Revision of the RLD Labeling" (2000)). In light of the range of timeframes in which ANDA holders currently submit such labeling supplements, we are proposing to revise these regulations to clarify FDA's expectations regarding the timeframe for submission of conforming labeling changes.

Proposed § 314.70(c)(8)(iv) states that upon FDA approval of changes to the labeling of the RLD, or if approval of the NDA for the RLD has been withdrawn under § 314.150, upon

FDA approval of changes to the labeling of an ANDA that relied on the RLD, any other ANDA holder that relied upon the RLD must submit a CBE-0 supplement with conforming labeling revisions within 30 days of FDA's posting of the approval letter for the labeling change on FDA's Web site, unless FDA requires the ANDA holder's labeling revisions at a different time in accordance with sections 505(o)(4) or 505-1 of the FD&C Act, or other applicable authority.

The ANDA holder would be expected to submit updated labeling for posting on <http://labels.fda.gov> and DailyMed at the time of submission of the CBE-0 supplement.

However, we recognize that distribution of drug products accompanied by an updated package insert may take additional time, depending on how often the drug is packaged, the size of manufacturer inventories, and other factors. Accordingly, proposed § 314.70(c)(8)(iv) is directed to prompt distribution of revised labeling in electronic format, and timely distribution of drug product accompanied by an updated package insert as soon as feasible thereafter or at the time of next printing of the product labeling for packaging.

FDA may require an ANDA holder to submit revised product labeling at a different time for safety labeling changes required under section 505(o)(4) of the FD&C Act or for REMS under section 505-1 of the FD&C Act. This may occur, for example, in the context of approval of modifications to a single, shared system REMS that are made to conform to safety labeling changes (see section 505-1(i)(1)(B) of the FD&C Act).

2. Changes to Highlights of Prescribing Information (Proposed §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2))

We are proposing to revise §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2) to remove the limitation on submission of CBE-0 supplements for changes to the Highlights of drug labeling in the PLR format.

Current §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2) exclude most changes to the information required in the Highlights, which are classified as a "major change" that must be made by a prior approval supplement, unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request under § 314.90. This exception reflected the Agency's earlier view that FDA review and approval of most proposed changes to the information in the Highlights of labeling was necessary because of the difficulty involved in summarizing the complex information presented in the full prescribing information (see "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 71 FR 3922 at 3932, January 24, 2006).

Based on our experience implementing the PLR, we have found this restriction on CBE-0 supplements to be unnecessary in practice. In response to an applicant's inquiry about submission of a CBE-0 supplement for a change that would affect the Highlights of drug labeling, FDA typically waives this limitation under § 314.90 or specifically requests that the applicant proceed with a CBE-0 supplement under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(i)(E).

The Highlights of drug labeling is intended to summarize the information that is most important for prescribing the drug safely and effectively. The types of newly acquired information that would otherwise meet the criteria for submission of a CBE-0 supplement include the critical safety information that is presented in the Highlights. Accordingly, we believe that limiting the availability of CBE-0 supplements for changes to the Highlights of drug labeling in the PLR format may pose an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications). Compare 50 FR 7452 at 7470, February 22, 1985 (stating that substantive changes in labeling 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").

Our proposal to remove the limitation on submission of CBE-0 supplements for changes to the Highlights also would create parity between application holders for drugs with labeling in the older format and application holders for drugs with PLR labeling. For example, this proposal would eliminate differences in the ability of application holders to submit CBE-0 supplements for a new or substantively revised contraindication based solely on whether current labeling appeared in the older format or PLR format.

We also are proposing to make conforming revisions to § 314.70(b)(2)(v)(C) to clarify that a prior approval supplement is required for any changes to the Highlights of drug labeling other than changes under § 314.70(c)(6)(iii), except for the specified changes that may be reported in an annual report.

3. Clarifying Revisions and Editorial Changes

We are proposing to revise the title to § 314.70(c) to refer to CBE-0 supplements to clarify the scope of paragraph (c). As revised, § 314.70(c) would describe changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (CBE-30 supplements) and certain changes being effected pending supplement approval (CBE-0 supplements). We also are proposing to add titles to paragraphs (c)(1) through (c)(7) of § 314.70 for clarity.

We are proposing to revise § 314.70(c)(1) to clarify that submission of a CBE-0 supplement is required for any change in the labeling to reflect newly acquired information of the type described in § 314.70(c)(6)(iii). The current text of § 314.70(c)(1) is directed only to

submission of supplements for certain manufacturing changes and does not fully describe the range of supplements for moderate changes that are described by this paragraph.

We are proposing to move the statement regarding the contents of a CBE supplement for certain manufacturing changes from existing § 314.70(c)(4) to § 314.70(c)(3) without changes.

We are proposing to revise § 314.70(c)(6)(iii) to clarify that an NDA holder or ANDA holder may distribute the drug product with revised labeling upon "submission" to FDA of the CBE-0 supplement for the labeling change, rather than upon FDA's "receipt" of the change. For ANDAs, section 744B(a)(5) of the FD&C Act (21 U.S.C. 379j-42(a)(5)) clarifies the time when a supplement is "submitted" to FDA, whereas the term "received" has a specific meaning that generally refers to FDA's determination that a submitted application has met certain criteria for completeness (see 21 CFR 314.101). This proposed revision is intended to avoid potential confusion, and more clearly establish the date on which distribution of revised labeling may occur.

B. Approval of Supplements to an Approved ANDA for a Labeling Change (Proposed § 314.97(b))

We are proposing to revise § 314.97 by designating the current text as paragraph (a) and by adding proposed paragraph (b) to clarify the process for approval of a supplement to an approved ANDA for a labeling change. Proposed § 314.97(b) explains that a supplement to an approved ANDA for a safety-related labeling change that is submitted in a prior approval supplement under § 314.70(b) or in a CBE-0 supplement under § 314.70(c)(6) will be approved upon approval of the same labeling change for the RLD, except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's prior approval supplement or CBE-0 supplement.

It has been FDA's longstanding position that an ANDA holder may submit a prior approval supplement to request a change to product labeling, and "FDA will determine whether the labeling for the generic and [reference] listed drugs should be revised" (57 FR 17950 at 17961, April 28, 1992; see also 57 FR 17950 at 17965 (describing requirement for "ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports or initiated any labeling changes") (emphasis added)). Proposed § 314.97(b) would expressly state that a prior approval supplement to an ANDA for a safety-related change in product labeling will be approved upon approval of the same labeling for the RLD. This approach ensures that the approved labeling for a generic drug continues to be the same as the approved labeling of its RLD (see section 505(j)(2)(A)(v) of the FD&C Act). If approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's prior approval supplement for a safety-related labeling change (see § 314.105; see also proposed § 314.70(c)(8)(iv)).

Similarly, FDA would approve a CBE-0 labeling supplement to an ANDA upon the approval of the same labeling change for the RLD (see section 505(j)(2)(A)(v) of the FD&C Act), except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's CBE-0 supplement (see § 314.105; see also proposed § 314.70(c)(8)(iv)). As explained in section I.B, FDA may accept, reject, or request modifications to the labeling changes proposed in the CBE-0 supplement. FDA's evaluation of the labeling change proposed by the ANDA holder would consider any submissions related to the proposed labeling change from the NDA holder for the RLD and from any other NDA or ANDA holders for drug products containing the same active ingredient. The Agency intends to act expeditiously, taking into account the reliability of the data, the magnitude and seriousness of

the risk, and number of CBE-0 supplements, and reach a decision on the approvability of labeling proposed by ANDA and NDA holders regarding the safety issue at the same time. After approval of a labeling change, other ANDA holders would be required to submit any necessary conforming labeling changes in accordance with proposed § 314.70(c)(8)(iv).

C. Exception for ANDA Labeling Differences Resulting From "Changes Being Effected"

Supplement (Proposed § 314.150(b)(10)(iii))

We are proposing to revise § 314.150(b)(10) to provide an additional exception regarding circumstances in which FDA may seek to withdraw approval of an ANDA based on generic drug labeling that is no longer consistent with the labeling for the RLD. Proposed § 314.150(b)(10)(iii) would include, as a permissible difference, changes to generic drug labeling under a CBE-0 supplement, with the understanding that such differences generally will be temporary.

This proposed exception reflects the Agency's judgment that concerns related to temporary differences in labeling between generic drugs and their RLDs are outweighed by the benefit to the public health that would result from all application holders having the ability to independently update drug product labeling to reflect newly acquired information regarding important drug safety issues through CBE-0 labeling supplements (compare section 505(j)(10) of the FD&C Act).

III. Legal Authority

FDA's legal authority to modify §§ 314.70, 314.97, 314.150, and 601.12 arises from the same authority under which FDA initially issued these regulations. The FD&C Act (21 U.S.C. 301 et seq.) and the PHS Act (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to

facilitate FDA's review and approval of applications regarding the labeling for those products. Section 502 of the FD&C Act (21 U.S.C. 352) provides that a drug or biological product 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); see also 42 U.S.C. 262(j)). Under section 502(f) of the FD&C 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 FD&C 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 FD&C Act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505(c) of the FD&C 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. Under section 505(j) of the FD&C Act, FDA will approve an ANDA only if the drug is, with limited exceptions, the same as a drug previously approved under section 505(c) of the FD&C Act with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD.

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 prohibits any person from falsely labeling any package

or container of a biological product. FDA's regulations in 21 CFR part 201 apply to all prescription drug products, including biological products.

In addition, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's regulations relating to CBE-0 supplements are supported by this provision. In 1965, FDA determined that, in the interest of drug safety, manufacturers should make certain safety-related changes to their product labeling at the earliest possible time (see 30 FR 993, January 30, 1965). Thus, for nearly 50 years, FDA, as the Agency entrusted with administration and enforcement of the FD&C Act and the protection and promotion of the public health, has required NDA holders, and subsequently BLA holders, to update drug product labeling with important, newly acquired safety information through submission of a CBE-0 supplement.

FDA's authority to extend the CBE-0 supplement process for safety-related labeling changes to ANDA holders arises from the same authority under which our regulations relating to NDA holders and BLA holders were issued. Nothing in the Hatch-Waxman Amendments or subsequent amendments to the FD&C Act limits the Agency's authority to revise the CBE-0 supplement regulations to apply to ANDA holders to help ensure that generic drugs remain safe and effective under the conditions of use prescribed, recommended, or suggested in the labeling throughout the life cycle of the generic drug product.

In Pliva v. Mensing, the Supreme Court recognized that "Congress and the FDA retain the authority to change the law and regulations if they so desire" (131 S. Ct. 2567, 2582). Recently, in Mutual Pharmaceutical Co., Inc. v. Bartlett, 133 S. Ct. 2466 (2013), the Court indicated that "Congress' decision to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying

either the drugs' compositions or their warnings" contributed to the outcome in that case (preemption of the tort claim against the generic manufacturer). We do not read this language to suggest that the Agency would not have authority to extend the CBE-0 supplement process to ANDA holders. The changes proposed in this rulemaking are authorized under the FD&C Act, which provides authority for FDA to permit NDA holders and BLA holders to change their product labeling to include certain newly acquired safety-related information through submission of a CBE-0 supplement.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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 would not be an economically significant regulatory action as defined by Executive Order 12866.

If a rule has a significant economic impact on a substantial number of small businesses, the Regulatory Flexibility Act requires Agencies to analyze regulatory alternatives that would minimize any significant impact of a rule on small entities. FDA has determined that this proposed rule would 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 \$141 million, using the most current (2012) 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 public health benefits from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing health care providers and the public could be improved. The proposed rule may reduce the time in which ANDA holders make safety-related labeling changes for generic drugs for which approval of the NDA for the RLD has been withdrawn. In addition, the proposed rule generally would reduce the time in which all ANDA holders make safety-related labeling changes, by requiring such ANDA holders to submit conforming labeling changes within 30 days of FDA's posting of the approval letter for the RLD's labeling change on its Web site. The primary estimate of the costs of the proposed rule includes costs to ANDA and NDA holders for submitting and reviewing CBE-0 supplements. We assume that the proposed rule will have no effect on the number of CBE-0 supplements submitted by BLA holders.

The proposed rule is expected to generate little cost. The Agency estimates the net annual social costs to be between \$4,237 and \$25,852. The present discounted value over 20 years would be in the range of \$63,040 to \$384,616 at a 3 percent discount rate, and in the range of \$44,890 to \$273,879 at a 7 percent discount rate.

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. This proposed rule would only impose new burdens on small generic drug manufacturers who submit CBE-0 supplements for safety-related labeling changes. Given the small cost per submission and the uncertainty in the estimated number of CBE-0 labeling supplements for safety-related labeling changes that may be submitted by an ANDA holder, we do not expect this proposed rule to impose a significant impact on a substantial number of small entities. We therefore propose to certify that that this proposed rule would not have a significant economic impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the PRA (44 U.S.C. 3501-3520). A description of these provisions is given in this document with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

Description: The proposed rule would permit ANDA holders to submit a CBE-0 supplement for certain types of labeling changes based on newly acquired information. At the time of submission, the ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless the NDA for the RLD has been withdrawn.

Description of Respondents: Respondents to this collection of information are NDA holders, ANDA holders, and BLA holders.

Burden Estimates: FDA regulations at §§ 314.70 and 314.97 set forth the requirements for submitting supplements to FDA for certain changes to an approved NDA or ANDA. These regulations specify the submission of supplements at different times, depending on the change to the approved application. Under § 314.70(c)(6), an applicant may commence distribution of a drug product upon receipt by FDA of a supplement for a change to the applicant's approved application (a CBE-0 supplement). The changes for which a CBE-0 supplement may be submitted include, among other things, changes in the labeling (§ 314.70(c)(6)(iii)) to reflect newly acquired information, for example, to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association.

FDA currently has OMB approval (OMB control number 0910-0001) for the submission of supplements to FDA for changes to an approved NDA or ANDA under §§ 314.70 (including § 314.70(c)(6)(iii)) and 314.97.

Under the proposed rule, ANDA holders would be permitted to submit a supplement to FDA for certain types of labeling changes based on newly acquired information. This collection

of information is not currently approved under OMB control number 0910-0001. Under proposed § 314.70(c)(8), if an NDA holder or ANDA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii), the NDA holder or ANDA holder should submit a CBE-0 supplement to FDA. Proposed § 314.70(c)(8) is intended to permit ANDA holders to update product labeling promptly, without FDA's special permission and assistance, to reflect newly acquired information that meets the criteria described in § 314.70(c)(6)(iii) irrespective of whether the revised labeling differs from that of the RLD.

To minimize confusion and make safety-related changes to generic drug labeling readily available to prescribing health care providers and the public while FDA is reviewing a CBE-0 supplement, FDA would establish, under proposed § 314.70(c)(8), a dedicated Web page (or, alternatively, a modification of an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement. ANDA holders would be required to verify that the correct information regarding the labeling changes proposed in their CBE-0 supplement appears on the FDA Web page. If the information is incorrect, the ANDA holder must contact the appropriate FDA review division within 2 business days of posting on the FDA Web page.

At the time of submission of the CBE-0 labeling supplement to FDA, proposed § 314.70(c)(8)(ii) would require the ANDA holder to send notice of the labeling change proposed in the supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless the NDA for the RLD has been withdrawn.

Based on the data summarized in section IV (Analysis of Impacts), we estimate that a total of approximately 15 ANDA holders ("number of respondents" in table 1) would submit to

us annually a total of approximately 20 CBE-0 labeling supplements under proposed § 314.70(c)(8), if this rule is finalized ("total annual responses" in table 1). We also estimate that preparing and submitting each CBE-0 labeling supplement under proposed § 314.70(c)(8) will take approximately 12 hours per ANDA holder ("hours per response" in table 1). This burden hour estimate includes the time needed by an ANDA holder to verify, as required under proposed § 314.70(c)(8), that the correct information regarding the labeling change proposed in its CBE-0 supplement appears on the FDA Web page, and the time needed to contact FDA if the information is incorrect.

In addition, we estimate that a total of approximately 15 ANDA holders would send notice of the labeling change proposed in each of the 20 CBE-0 labeling supplements, including a copy of the information supporting the change, to the NDA holder for the RLD, as required under proposed § 314.70(c)(8)(ii). We also estimate that preparing and sending each notice would take approximately 3 hours per ANDA holder.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
CBE-0 supplement submission by ANDA holders (314.70(c)(8))	15	1.34	20	12	240
ANDA holder notice to NDA holder (314.70(c)(8)(ii))	15	1.34	20	3	60
Total					300

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7245, or emailed to oir_submission@omb.eop.gov. All

comments should be identified with the title, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products."

In compliance with the PRA (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register.

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) and 25.31(a) and (g) 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.

VII. Effective Date

FDA proposes that any final rule based on this proposal become effective 30 days after the date of its publication in the Federal Register.

We intend to apply this rule, if finalized, to any submission received by FDA on or after the effective date. This proposed rule provides sufficient notice to all interested parties, including NDA holders, ANDA holders, and BLA holders, to adjust their submissions and actions by the time we issue any final rule. However, we invite comments on how a final rule should be implemented.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship

between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

X. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site address in this reference section, but we are not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

1. IMS Institute for Healthcare Informatics, "The Use of Medicines in the United States: Review of 2011," April 2012 (available at http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf).

2. Lester J., G. A. Neyarapally, E. Lipowski, et al., "Evaluation of FDA Safety-Related Drug Label Changes in 2010," Pharmacoepidemiology Drug Safety, vol. 22, pp. 302-305, 2013.

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.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR parts 314 and 601 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.

§ 314.70 [Amended]

2. Amend § 314.70 as follows:

- a. Revise paragraph (b)(2)(v)(C) introductory text;
- b. Revise the paragraph (c) heading;
- c. Add headings to paragraphs (c)(1) through (c)(7);
- d. Revise paragraphs (c)(1), (c)(3), (c)(4), (c)(6) introductory text, (c)(6)(iii) introductory text, and (c)(7); and

e. Add new paragraph (c)(8).

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(2) * * *

(v) * * *

(C) Any change to the information required by § 201.57(a) of this chapter other than changes under paragraph (c)(6)(iii) of this section, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

* * * * *

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change and certain changes being effected pending supplement approval (moderate changes).

(1) Types of changes for which a supplement is required. A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. A supplement also must be submitted for any change in the labeling to reflect newly acquired information of the type described in paragraph (c)(6)(iii) of this section. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (changes being effected in 30 days). * * *

* * * * *

(3) Explanation of basis for the change and supplement identifier. A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement--Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement--Changes Being Effected." The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(4) Distribution of drug product pending supplement approval (for changes being effected in 30 days). Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

(5) Limitations on distribution of drug product pending supplement approval (for changes being effected in 30 days). * * *

* * * * *

(6) Changes requiring supplement submission prior to distribution of the drug product made using the change (changes being effected). The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon submission to the agency of a supplement for the change. These changes include, but are not limited to:

(i) * * *

(ii) * * *

(iii) Changes in the labeling to reflect newly acquired information to accomplish any of the following:

* * * * *

(7) Effect of complete response letter for changes being effected supplement. If the agency issues a complete response letter to the supplemental application, the manufacturer may be ordered to cease distribution of the drug product(s) made with the manufacturing change or, if the supplemental application was submitted for a labeling change under paragraph (c)(6) of this section, the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling.

(8) Equal applicability to application holders and abbreviated application holders. An application holder may submit to its approved application or abbreviated application a supplement described by paragraph (c)(6)(iii) of this section. FDA will promptly post on its Web site information regarding the labeling changes proposed in the changes being effected supplement. The applicant must verify that the correct information regarding the labeling changes proposed in the changes being effected supplement appears on FDA's Web site and must contact FDA within 5 business days of posting if the information is incorrect.

(i) Contents of supplement. A supplement to an approved application or abbreviated application described by paragraph (c)(6)(iii) of this section must contain the following information:

(A) The application number(s) of the drug product(s) involved;

(B) A description of the labeling change proposed in the changes being effected supplement;

(C) The basis for the labeling change proposed in the changes being effected supplement, including the data supporting the change or, if submitted under paragraph (c)(6)(iii)(E), the specific change requested by FDA;

(D) A copy of the final printed labeling and current product labeling annotated with the labeling change proposed in the changes being effected supplement;

(E) If the changes being effected supplement is submitted by an abbreviated application holder and approval of the application for the reference listed drug has not been withdrawn under § 314.150 of this chapter, a statement confirming that the notice described in paragraph (c)(8)(ii) of this section has been sent to the application holder for the reference listed drug.

(ii) Notice of labeling changes being effected. An abbreviated application holder must send notice of the labeling change proposed in the changes being effected supplement, including a copy of the information supporting the change (with any personally identifiable information redacted), to the application holder for the reference listed drug at the same time that the supplement to the abbreviated application is submitted to FDA, unless approval of the application has been withdrawn under § 314.150 of this chapter. An application holder or any abbreviated application holder may submit (on its own initiative or in response to a request from FDA) a labeling supplement or correspondence to its application or abbreviated application, as applicable, regarding the proposed labeling changes.

(iii) Distribution of revised labeling. Pending approval of the supplement by FDA, distribution of the drug product with the revised labeling may be made by an application holder or abbreviated application holder upon submission to FDA of the supplement, except that if FDA determines during its review period that the supplement does not meet the criteria described in paragraph (c)(6)(iii) of this section, the supplement will be converted to a prior approval

supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling.

(iv) Conforming labeling requirements. Upon FDA approval of changes to the labeling of the reference listed drug or, if the application for the reference listed drug has been withdrawn, upon FDA approval of changes to the labeling of an abbreviated application that relied on the reference listed drug, any other abbreviated application holder that relied upon the reference listed drug must submit a supplement under paragraph (c)(6)(iii)(E) of this section with conforming labeling revisions within 30 days of FDA's posting of the approval letter on its Web site, unless FDA requires the abbreviated application holder's labeling revisions at a different time in accordance with sections 505(o)(4) or 505-1 of the Federal Food, Drug, and Cosmetic Act.

* * * * *

§ 314.97 [Amended]

3. Revise § 314.97 to read as follows:

§ 314.97 Supplements and other changes to an approved abbreviated application.

(a) The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

(b) A supplement to an approved abbreviated application for a safety-related change in the labeling that is submitted under § 314.70(b) or (c)(6) will be approved upon approval of the same labeling change for the reference listed drug, except that if approval of the application for the reference listed drug has been withdrawn under § 314.150, FDA may approve such a supplement to an approved abbreviated application.

§ 314.150 [Amended]

4. Amend § 314.150 as follows:

a. In paragraph (b)(10)(i), remove the word "or";

b. In paragraph (b)(10)(ii), remove the period and replace with a semicolon followed by the word "or"; and

c. Add paragraph (b)(10)(iii).

§ 314.150 Withdrawal of approval of an application or abbreviated application.

* * * * *

(b) * * *

(10) * * *

(iii) Changes to the labeling for the drug product that is the subject of the abbreviated application under § 314.70(c)(6)(iii) of this chapter.

* * * * *

PART 601--LICENSING

5. 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).

6. Amend § 601.12 by revising paragraphs (f)(1), (f)(2)(i) introductory paragraph, and (f)(2)(ii); and by adding new paragraph (f)(2)(iii) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * * (1) Labeling changes requiring supplement submission--FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the labeling. An applicant may report the minor changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(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 to accomplish any of the following:

* * * * *

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted, except that if FDA determines during its review period that the supplement does not meet the criteria described in paragraph (f)(2)(i) of this section, the supplement will be converted to a prior approval supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: "Special Labeling Supplement--Changes Being Effected."

(iii) FDA will promptly post on its Web site information regarding the labeling changes proposed in the changes being effected supplement. The applicant must verify that the correct information regarding the labeling changes proposed in the changes being effected supplement appears on FDA's Web site and must contact FDA within 5 business days of posting if the information is incorrect.

* * * * *

Dated: November 5, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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