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CHANGES BEING EFFECTED TO DRUG LABELING REGIME: FDA RELEASES PROPOSED PATHWAY FOR GENERIC SAFETY UPDATES

On November 13, the U.S. Food and Drug Administration ("FDA") published a proposed rule concerning "procedures for application holders of an approved drug or biological product to change the product labeling to reflect certain types of newly acquired information prior to FDA's review of the change" that would, specifically, allow abbreviated new drug application ("ANDA") holders to update product labeling for their "generic" drug products in advance of its reference listed drug ("RLD"; i.e., the approved drug product to which the generic version was compared to show bioequivalence).[1] FDA's proposal would permit—for the first time—a generic drug product label to differ from the RLD product label, ostensibly for a limited and temporary time period.

BACKGROUND

The proposed rule changes a long-standing industry standard that a generic product's label match that of the RLD, with the RLD holder primarily driving label changes. FDA has generally taken the position that a generic drug must maintain the same labeling as the RLD through the generic product's lifecycle. A generic drug is required to have and maintain the same labeling as the RLD, except for changes required because of a difference approved under a suitability petition or because the generic and RLD are produced or distributed by different manufacturers. The few permissible differences contemplated by this latter category are described by regulation.

1 78 Fed. Reg. 67985 (Nov. 13, 2013).

FDA's proposed amendments are, in part, a response to recent Supreme Court decisions, *Wyeth v. Levine*, 555 U.S. 555 (2009), *Pliva, Inc. v. Mensing*, 131 S.Ct. 2567 (2011), and *Mutual Pharmaceutical Co., Inc. v. Barlett*, 570 U.S. – (2013), pertaining to generic drug companies' insulation from state law tort claims due to the federal labeling requirements, and an August 2011 Citizen Petition (Docket No. FDA-2011-P-0675), requesting that FDA amend regulations to establish a requirement for generic drug companies to update product labels to ensure drug labeling provides warnings based on new information. FDA responded to the Citizen Petition at the same time it issued the pre-publication regarding the proposed rule, granting the petition in part and stating in its response that the proposed amendments set forth in the Federal Register would address some of the requested revisions to the regulations. (For a discussion regarding the Supreme Court cases and the possible implications regarding state law tort claims, please *see Jones Day Commentary* entitled "FDA Proposed Drug Safety Warning Rule that May Eliminate Preemptions Defenses in Some Failure-to-Warn Cases," *available at* www.jonesday.com/fda-proposes-drug-safety-warning-rule-that-may-eliminate-preemption-defenses-in-some-failure-to-warn-cases-11-15-2013/.)

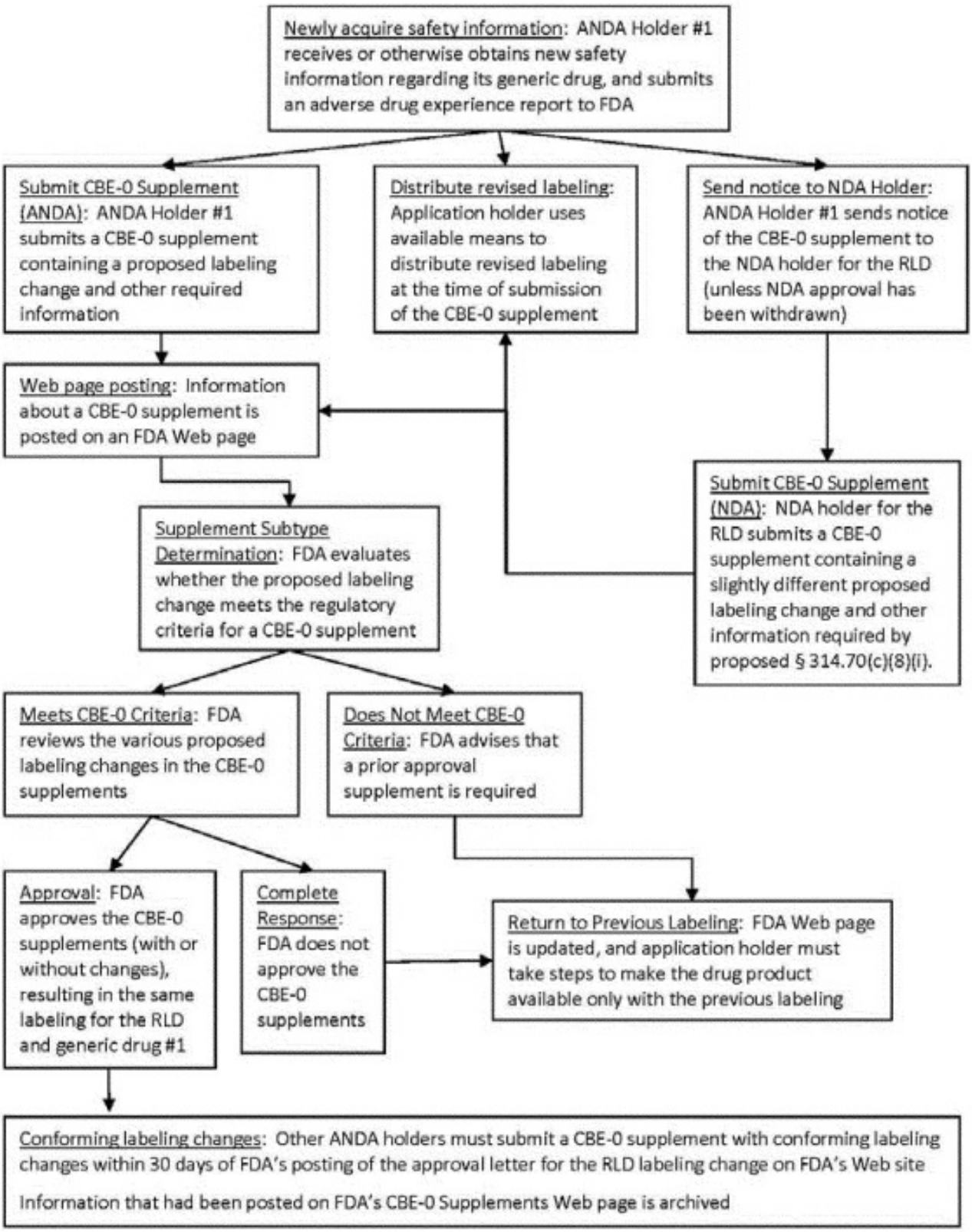
PROPOSED REGULATORY PATHWAY AND PROCEDURES

If the proposed rule were to be implemented without changes, an ANDA holder would be authorized to submit a "changes being effected" ("CBE-0") supplement to update a generic drug label to reflect certain newly acquired information regardless of whether the updated label differs from the RLD label. New drug application ("NDA") holders have had a basis for updating their labels under a CBE-0 supplement for decades, although FDA has revised and clarified the policy and rules over time. Stating the Agency is creating parity among application holders, the proposed rule would explicitly extend the mechanism beyond NDA holders to permit ANDA holders to submit CBE-0 supplements to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is satisfactory causal association; to add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; to add or strengthen an instruction about dosage and administration that is intended to increase the product's safe use; to delete false, misleading, or unsupported indications for use or effectiveness claims; or any labeling change normally requiring a supplement and FDA approval that FDA specifically requests.

The proposed amendments would require a CBE-0 supplement to contain the following information: (i) the application number(s) of the drug product(s) for which the CBE-0 supplement is being submitted: (ii) a description of the proposed labeling change; (iii) the basis for the proposed labeling change; (iv) a copy of the proposed product labeling; and (v) for an ANDA holder, confirmation that notice of the proposed labeling change in the CBE-0 supplement, including a copy of the information supporting the change, has been sent to the NDA holder for the RLD at the same time that the ANDA supplement is submitted to FDA, unless the approval of the NDA has been withdrawn.

Providing the ANDA holder CBE-0 authority would require a new procedure for coalescing product labels, particularly where multiple generics are available for one RLD or where the RLD has been discontinued. FDA has crafted one example of how the procedure may work. *See* Figure 1 on page 3 from the Federal Register.

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



FDA proposes that the ANDA recipient of newly acquired safety information (following submission of adverse event information, as appropriate) would simultaneously: (i) submit a CBE-0 supplement in the form described, (ii) distribute revised labeling at the time of submission, and (iii) notify the NDA holder of the RLD, if any.

To make the proposed labeling change information available to prescribers and patients as quickly as possible, FDA proposes to post the CBE-0 information to an FDA website, immediately and without review of the supplement information. The submitter would be responsible for verifying that the correct CBE-0 supplement information appears on the webpage and for contacting FDA within five business days of the posting if the information is incorrect. The webpage posting of the supplement would continue during FDA's review of the proposed labeling change and determination of whether the change meets the criteria for a CBE-0. The supplement would be available on the webpage until FDA has completed its review and issued an action letter.

FDA explains that a copy of the information supporting the labeling change described in the CBE-0 supplement should be sent to the NDA holder because the NDA holder, in most cases, has substantial knowledge about the post-marketing experience of the drug product and "FDA's analysis of whether the labeling changed 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 the ANDA submission."[2] The NDA holder would independently review the information contained in the notification from the generic company and may submit a labeling supplement or correspondence to its NDA regarding the change proposed by the CBE-0. If the NDA holder for the RLD does not submit a supplement seeking approval for a label change that is related or conforming to that in the CBE-0 supplement, FDA may request that the NDA holder submit such a supplement. Indeed, FDA states in the description of the proposed rule that "[i]t 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 … [I]f 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."[3]

If the proposed change meets the criteria for a CBE-0 supplement and FDA approves the change, both the ANDA submitter's and RLD label revision would be approved at the same time. These changes to the RLD label would require other ANDA holders to update their labels with conforming language via a CBE-0 within 30 days of posting of the RLD labeling change to the FDA website. However, if the Agency were to issue a complete response not approving the CBE-0, the application holder(s) must revert to the previous product labeling and cease distribution of the product with the revised label.

FDA REQUESTING COMMENT

FDA is requesting comments on the proposed rule, including specifically the proposed approach for informing prescribers and patients of proposed labeling changes for a particular generic product via a new or existing webpage and whether five business days is sufficient for an applicant to verify the accuracy and completeness of posted information. FDA is proposing the rule become effective 30 days after the date of final publication. Thus, FDA intends the proposed rule, if finalized, to apply to any submission received by FDA on or after the effective date. However, FDA has invited comments on how the final rule should be implemented. FDA has established a 90-day docket for the collection of comments; interested individuals may submit electronic or written comments through January 13, 2014.

2 78 Fed. Reg. at 67991.

3 78 Fed. Reg. at 67992-3.

LAWYER CONTACTS

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