Guidance for Industry

Public Availability of Labeling Changes in "Changes Being Effected" Supplements

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Meredith Francis 301-594-2041.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2006
Labeling

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Guidance for Industry[1] Public Availability of Labeling Changes in "Changes Being Effected" Supplements

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance announces to holders of a new drug application (NDA), an abbreviated new drug application (ANDA), or a biologics license application (BLA), who intend to submit a "Changes Being Effected" supplement (CBE supplement) to make a postapproval labeling change, that FDA will make labeling revisions identified in a CBE supplement publicly available upon receipt of the supplement by FDA.[2] This guidance does not have any bearing on supplements that relate to chemistry, manufacturing, and controls changes.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA has begun an initiative to facilitate computerized access to drug information by consumers, pharmacists, and healthcare providers so that they will have faster and more comprehensive

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food ad Drug Administration.

[2] While the FDA will make labeling revisions submitted via a CBE supplement publicly available when they are received by the FDA, this action should not be construed as an endorsement of the revised labeling by the FDA. As noted in section III, after revised labeling is submitted, the FDA carefully reviews the proposed change and then either approves it or sends a letter identifying the deficiencies with the proposed change. Of particular note, the Agency will not permit a labeling change that would misbrand the product (see footnote 4).

access to drug information. As part of this initiative, the Agency has been involved in an initiative known as *DailyMed*. DailyMed is a computerized repository of a broad array of drug information, which is maintained by the National Library of Medicine. Among other things, DailyMed contains the information referred to as "content of labeling," which includes all the information found in prescription drug labeling and over-the-counter (OTC) drug facts labeling, including all text, tables, and figures (see 21 CFR 314.50(l)(i)). To maximize its ability to serve as a useful resource to consumers, pharmacists, and healthcare providers, DailyMed must contain the most up-to-date and comprehensive drug information available. This guidance discusses FDA policy with regard to the timing of our release of revised drug labeling information.

Sections 314.70 and 601.12 (21 CFR 314.70 and 601.12) of FDA's regulations describe the types of supplemental applications that must be submitted to FDA to effect a labeling change to approved NDAs, ANDAs, and BLAs. Certain types of changes to labeling must receive FDA approval before the changes are implemented. These include all labeling changes that do not fall under § 314.70(c)(6)(iii), (d)(2)(ix), or (d)(2)(x), or under § 601.12(f)(2) or (f)(3). Other changes may be implemented by a sponsor upon the Agency's receipt of a CBE supplement (§§ 314.70(c)(6)(iii) and 601.12(f)(2)(i)). Under §§ 314.70(c)(6)(iii) and 601.12(f)(2)(i), the labeling changes appropriate for CBE supplements are those that: (1) add or strengthen a contraindication, warning, precaution, or adverse reaction; (2) add or strengthen a statement about abuse, dependence, psychological effect, or overdosage; (3) add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; (4) delete false, misleading, or unsupported indications for use or claims for effectiveness; or (5) normally require a supplement submission and approval before distribution of the product and that FDA specifically requests be submitted under these provisions.[3]

III. DISCUSSION

After a CBE supplement is submitted, FDA reviews the proposed change and either approves it or sends a letter identifying the deficiencies with the proposed change.[4] Historically, most sponsors have implemented the proposed labeling changes at the time of, or shortly after, the Agency's receipt of the CBE supplement. However, some have delayed implementation until they receive FDA feedback before implementing any change.

In the past, FDA has not made any labeling change proposed in a CBE supplement publicly available until it has been approved. However, this policy could lead to situations where a

[3] As explained in the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," that we published in the *Federal Register* on January 24, 2006 (71 FR 3922), a sponsor may not use a CBE supplement to change the "Highlights of Prescribing Information" section except for editorial or similar minor changes. For a more complete discussion on this point, see 71 FR at 3932 and 3934.

[4] Congress has charged FDA with ensuring, among other things, that drugs sold in the United States are not misbranded (21 U.S.C. 331(a), (b), and (k); 321(n); 352; and 355(c) and (d)(7)). Consistent with the Federal Food, Drug, and Cosmetic Act, FDA will not permit a change to labeling that would misbrand the product. For example, FDA would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event.

company, in compliance with the regulations, is distributing labeling that contains updated safety information while FDA is not making the updated version of the labeling available.

To avoid this situation and to facilitate the DailyMed initiative, FDA wants to make the most current labeling submitted to FDA available to healthcare practitioners and the public. Therefore, FDA is announcing its intention to change its practice with regard to making labeling changes submitted in CBE supplements -- but not in prior approval supplements -- publicly available.

This guidance announces 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. If, after reviewing the CBE supplement, FDA decides it should not be approved, FDA will either (1) remove the labeling submitted with the CBE supplement from the FDA Web site and from the DailyMed and replace that labeling with the previous labeling or (2) recommend the sponsor amend its labeling and, after the sponsor submits the amended labeling, post this amended labeling on FDA's Web site and provide it to the DailyMed promptly.[5]

Given this new procedure, we recommend that a sponsor not submit a CBE supplement to FDA until the sponsor is ready to distribute the labeling that it proposes in that CBE supplement. FDA will consider the submission of a CBE supplement to be consent by the sponsor to post the proposed labeling on FDA's Web site and on the DailyMed. The Agency welcomes discussions with sponsors before they submit a CBE supplement.

[5] Nothing in this guidance is intended to expand the circumstances in which an applicant may effect labeling changes via a CBE supplement, and particularly, those pertaining to generic drugs.