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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99D-0529]

Agency Information Collection Activities; Submission for OMB Review; Comment Request; Guidance for Industry: Changes to an Approved NDA or ANDA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the proposed collection of information listed below has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995 (PRA).

DATES: Submit written comments on the collection of information by [*insert date 30 days after date of publication in the Federal Register*].

ADDRESSES: Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1482.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Guidance for Industry: Changes to an Approved NDA or ANDA

On November 21, 1997, the President signed into law the FDA Modernization Act (the Modernization Act) (Public Law 105-115). Section 116 of the Modernization Act amended the

Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a), which describes requirements and procedures for making and reporting manufacturing changes to approved new drug applications (NDA's) and abbreviated new drug applications (ANDA's), to new and abbreviated animal drug applications, and to license applications for biological products.

The guidance provides recommendations to holders of approved NDA's and ANDA's who intend to make postapproval changes in accordance with section 506A of the act. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in: (1) Components and composition, (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7) miscellaneous changes.

Section 116 of the Modernization Act amended the act by adding section 506A, which includes the following provisions:

1. A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the applicant validates the effects of the change on the identity strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug (section 506A(a)(1) and (b) of the act). This section recognizes that additional testing, beyond testing to ensure that an approved specification is met, is required to ensure unchanged identity, strength, quality, purity, or potency as these factors may relate to the safety or effectiveness of the drug.

2. A drug made with a major manufacturing change may be distributed only after the applicant submits a supplemental application to FDA and the supplemental application is approved by the agency. The application is required to contain information determined to be appropriate by FDA and include the information developed by the applicant when "validating the effects of the change" (section 506A(c)(1) of the act).

3. A major manufacturing change is a manufacturing change determined by FDA to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the

drug as these factors may relate to the safety or effectiveness of the drug. Such changes include:

(1) A change made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license unless exempted by FDA by regulation or guidance; (2) a change determined by FDA by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change; and (3) other changes determined by FDA by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug (section 506A(2) of the act).

4. FDA may require submission of a supplemental application for drugs made with manufacturing changes that are not major (section 506A(d)(1)(B) of the act) and establish categories of manufacturing changes for which a supplemental application is required (section 506A(d)(1)(C) of the act). In such a case the applicant may begin distribution of the drug 30 days after FDA receives a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required (section 506A(d)(3)(B)(i) of the act). FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change (section 506A(d)(3)(B)(ii) of the act). If FDA disapproves a supplemental application, the agency may order the manufacturer to cease the distribution of drugs that have been made with the disapproved change (section 506A(d)(3)(B)(iii) of the act).

5. FDA may authorize applicants to distribute drugs without submitting a supplemental application (section 506A(d)(1)(A) of the act) and may establish categories of manufacturing changes that may be made without submitting a supplemental application (section 506A(d)(1)(C) of the act). The applicant is required to submit a report to FDA on such a change and the report is required to contain information the agency deems to be appropriate and information developed by the applicant when validating the effects of the change. FDA also may specify the date on which the report is to be submitted (section 506A(d)(2)(A) of the act). If during a single year

an applicant makes more than one manufacturing change subject to an annual reporting requirement, FDA may authorize the applicant to submit a single report containing the required information for all the changes made during the year (annual report) (section 506A(d)(2)(B) of the act).

Section 506A of the act provides FDA with considerable flexibility to determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the guidance on section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have such an adverse effect. Conversely, a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely affect the product. The guidance enables the agency to respond more readily to knowledge gained from manufacturing experience, further research and data collection, and advances in technology. The guidance describes the agency's current interpretation of specific changes falling into the four filing categories. Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. The use of guidance documents allows FDA to more easily and quickly modify and update important information.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

Federal Food, Drug, and Cosmetic Act Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
506A(c)(1) and (c)(2) Prior approval supplement	594	3	1,744	120	209,280

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹—Continued

Federal Food, Drug, and Cosmetic Act Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
506A(d)(1)(C), and (d)(3)(B)(i) CBE ² in 30-day supplement	594	5	2,754	80	220,320
506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(ii) CBE ² supplement	486	1	486	80	38,880
506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B) Annual report	704	10	6,929	25	173,225
Total					641,705

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

²CBE means changes being effected.

Section 506A(a)(1) and (b) of the act requires the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. Under section 506A(d)(3)(A) of the act, information developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency is required to be submitted to FDA as part of the supplement or annual report. Thus, no separate estimates are provided for these sections in table 1 of this document; estimates for validation requirements are included in the estimates for supplements and annual reports. The guidance does not provide recommendations on the specific information that should be developed by the applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

Section 506A(c)(1) and (c)(2) of the act sets forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Under this section, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as the factors may relate to the safety or effectiveness of the product. The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using the change.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 1,744 supplements will be submitted annually under section 506A(c)(1) and (c)(2) of the act. FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 120 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i) of the act sets forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Under this section, a supplement must be submitted for any change in the 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 product as these factors may relate to the safety or effectiveness of the product. Distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

Based on the data concerning the number of supplements received by the agency, FDA estimates that approximately 2,754 supplements will be submitted annually under section 506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i) of the act. FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 80 hours to prepare and submit to FDA each supplement.

Under section 506A(d)(3)(B)(ii) of the act, FDA 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 upon receipt by the agency of a supplement for the change. Based on the data concerning the number of supplements received by the agency, FDA estimates that approximately 486 supplements will be submitted annually under section 506A(d)(3)(B)(ii) of the act. FDA estimates that approximately 486 applicants will submit such supplements, and that it will take approximately 80 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(A), (d)(1)(C), and (d)(2)(A), and (d)(2)(B) of the act sets forth requirements for changes to be described in an annual report (minor changes). Under this section, changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report.

Based on the data concerning the number of supplements and annual reports received by the agency, FDA estimates that approximately 6,929 annual reports will include documentation of certain manufacturing changes as required under section 506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B) of the act. FDA estimates that approximately 704 applicants will submit such information, and that it will take approximately 25 hours to prepare and submit to FDA the information for each annual report.

In the **Federal Register** of June 28, 1999 (64 FR 34608), FDA published a proposed rule to implement section 116 of the Modernization Act by revising current regulations at 21 CFR 314.70 on supplements and other changes to an approved application. In that same issue of the **Federal Register** (64 FR 34660), FDA published a notice of availability of a draft guidance for industry entitled "Changes to an Approved NDA or ANDA." On August 19, 1999, FDA held a public meeting to discuss and receive comments on the proposed regulations and the draft guidance (64 FR 42625, August 5, 1999).

The period for public comment on the proposed regulations closed on September 13, 1999 and FDA is currently reviewing the comments and preparing a final rule. The comment period for the draft guidance closed on August 27, 1999, and FDA has considered these comments when preparing the guidance that is the subject of this request.

FDA published in the **Federal Register** of January 6, 2000 (65 FR 779), a 60-day notice requesting comments on the extension of the proposed collection of information in this guidance. In response to this notice, no comments were received by the agency.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Dated: March 30, 2000



William K. Hubbard
Senior Associate Commissioner for
Policy, Planning, and Legislation

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