however, if FDA determines that such a voluntary recall is not effective in remedying a violation and there remains a reasonable probability that the violative device would cause serious adverse health consequences or death, FDA will invoke the medical device recall authority in addition to the voluntary efforts that the manufacturer has already undertaken. FDA will not order a mandatory recall if a voluntary recall has been effective in addressing the problems.

FDA believes that the November 1996 final rule provides sufficient flexibility so as to minimize the burden on those required to take action consistent with the determination that the device presents a risk of serious adverse health consequences or death. FDA expects that at most one or two recalls per year would be ordered that would not have occurred without this regulation.

In response to the comment regarding the use of electronic media for complying with these provisions, the regulation for electronic records and electronic signatures became effective March 20, 1997. Part 11 (21 CFR part 11) sets forth the criteria under which FDA will accept documents and signatures in electronic form in lieu of paper.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
810.10(d)	2	1	2	8	16
810.11(a)	1	1	1	8	8
810.12(a) and (b)	1	1	1	8	8
810.14	2	1	2	16	32
810.15(a) through (d)	2	1	2	16	32
810.15(e)	10	1	1	1	10
810.16	2	12	24	40	960
810.17	2	1	2	8	16
Total					1,082

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

FDA developed these estimates based on its experience with the number of voluntary recalls received in the last 3 years and other similar procedures.

Dated: October 27, 1999.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 99–28664 Filed 11–2–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99N–4614]

Agency Emergency Processing Request Under OMB Review; 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 a collection of information has been submitted to the Office of Management and Budget (OMB) for emergency processing under the Paperwork Reduction Act of 1995 (the PRA). The collection of information is contained in a guidance for industry entitled ''Changes to an Approved NDA or ANDA.'' The guidance is intended to assist applicants in determining how they should report changes to an approved new drug application (NDA) or abbreviated new drug application (ANDA) under section 116 of the Food and Drug Administration Modernization Act (the Modernization Act), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

DATES: Submit written comments on the collection of information by November 10, 1999.

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: Desk Officer for FDA. All comments should be identified with the docket number found in brackets in the heading of this document.

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: On November 21, 1997, the President signed the Modernization Act (Public Law 105–115) into law. 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 NDA's and ANDA's, to new and abbreviated animal drug applications, and to license applications for biological products.

The guidance for industry entitled ''Changes to an Approved NDA or ANDA'' provides recommendations to holders of 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.

With respect to the collection of information described below, FDA invites comment on: (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: Changes to an Approved NDA or ANDA

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 (sections 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.

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(c)(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 may also 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.

Description of Respondents: Businesses or other for-profit organizations.

As explained below, FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN [1]

Federal Food, Drug, and Cosmetic Act Sections	No. of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
506A(c)(1) 506A(c)(2) Prior approval supplement (supp.) 506A(d)(1)(B) 506A(d)(1)(C)	594	3	1,744	120	209,280

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN [1]—Continued

Federal Food, Drug, and Cosmetic Act Sections	No. of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
506A(d)(3)(B)(i) Changes being effected (CBE) in 30-day supp.	594	5	2,754	80	220,320
506A(d)(1)(B) 506A(d)(1)(C) 506A(d)(3)(B)(ii) CBE supp.	486	1	486	80	38,880
506A(d)(1)(A) 506A(d)(1)(C) 506A(d)(2)(A) 506A(d)(2)(B) Annual Report	704	10	6,929	25	173,225
Total					641,705

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

Sections 506A(a)(1) and 506A(b) of the act require 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), 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 the Table 1; 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.

Sections 506A(c)(1) and 506A(c)(2) of the act set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Under these sections, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial 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. 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 sections 506A(c)(1) and 506A(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.

Under section 506A(d)(1)(B), 506A(d)(1)(C), and 506A(d)(3)(B)(i) of the act set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Under these sections, 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 data concerning the number of supplements received by the agency, FDA estimates that approximately 2,754 supplements will be submitted annually under sections 506A(d)(1)(B), 506A(d)(1)(C), and 506A(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 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.

Sections 506A(d)(1)(A), 506A(d)(1)(C), 506A(d)(2)(A), and 506A(d)(2)(B) of the act set forth requirements for changes to be described in an annual report (minor changes). Under these sections, 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 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 sections 506A(d)(1)(A), 506A(d)(1)(C), 506A(d)(2)(A), and 506A(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. (On August 5, 1999, a notice of the meeting was published in the **Federal Register** (64 FR 42625).)

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 for emergency processing.

FDA is requesting emergency processing of this proposed collection of information under section 3507(j) of the PRA and 5 CFR 1320.13. The information is needed immediately to implement section 506A of the act, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The use of normal information clearance procedures would likely result in the prevention or disruption of this collection of information because section 506A takes effect on November 21, 1999. After November 20, 1999, and until final regulations are issued revising 21 CFR 314.70, section 506A of the act will be the sole basis for FDA's regulation of postapproval manufacturing changes for products approved under NDA's or ANDA's. 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. 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.

Dated: October 29, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–28793 Filed 11–2–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Training Programs for Regulatory Project Managers; Information Available to Industry

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is initiating of two new training programs: The Regulatory Project Manager Site Tours and the Regulatory Project Manager Shadowing Program. These programs are intended to give the Center for Drug Evaluation and Research's (CDER's) regulatory project managers an opportunity to tour pharmaceutical facilities and shadow their industry counterparts. Both the tour and shadowing programs are intended to enhance review efficiency and quality by providing CDER staff with a better understanding of the pharmaceutical industry and its operations. The purpose of this notice is to invite pharmaceutical companies interested in participating in these programs to contact CDER for more information.

DATES: Pharmaceutical companies may request training program information at any time.

FOR FURTHER INFORMATION CONTACT: Deborah L. Kallgren, Center for Drug Evaluation and Research (HFD–2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5481, FAX 301–827–3132.

SUPPLEMENTARY INFORMATION:

I. Background

An important part of CDER's commitment to make safe and effective drugs available to all Americans is optimizing the efficiency and quality of the drug review process. To support this primary goal, CDER has initiated various training and development programs to promote high performance in its regulatory project management staff. CDER seeks to significantly enhance review efficiency and review quality by providing the staff with a better understanding of the pharmaceutical industry and its operations. To this end, CDER is initiating two new training programs to give regulatory project managers the opportunity to tour pharmaceutical facilities and shadow their industry regulatory/project management counterparts. The goals are: (1) To provide first hand exposure to industry's drug development processes, and (2) to provide a venue for sharing information about project management procedures (but not drug-specific information) with industry representatives.

II. The Project Manager Site Tours and Regulatory Project Manager Shadowing Program

A. Regulatory Project Management Site Tours

In this program, over a 2-day period, small groups (six or less) of project managers accompanied by a senior level regulatory project manager may observe operations of pharmaceutical manufacturing, packaging facilities and pathology/toxicology laboratories, and regulatory affairs operations. The purpose of this tour, or any part of the program, is meant to improve mutual understanding and to provide an avenue for open dialogue.

B. Regulatory Project Manager Shadowing Program

In this program, over a 2- to 3-day visit, regulatory project managers will accompany their industry counterparts in their day-to-day activities. The primary objective of the shadowing program is to learn about the team approach to drug development, including drug discovery, preclinical evaluation, project tracking mechanisms, and regulatory submission operations. The overall benefit to regulatory project managers will be exposure to project management and team techniques and processes employed by the pharmaceutical industry, professional and personal growth, and enhanced job satisfaction and performance through increased understanding of the industry processes and procedures that directly relate to their jobs.

C. Site Selection

All travel expenses associated with the site tours and/or shadowing programs will be the responsibility of CDER, therefore, selection of potential facilities will be based on available resources for this program.

If your firm is interested in learning more about these training opportunities, please contact Deborah L. Kallgren (address above).

Dated: October 25, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–28564 Filed 11–2–99; 8:45 am]

BILLING CODE 4160–01–F