open to the public, limited only by the space available. The meeting room accommodates 80 people. Due to limited space, notification of intent to attend the meeting must be made to Diane Miller no later than Friday, April 16, 2004. Ms. Miller can be reached by telephone at 513/533–8450 or by email at *niocindocket@cdc.gov.* Requests to attend the meeting will be accommodated on a first-come basis.

Purpose: To discuss the health data relevant to titanium dioxide exposure and the scientific and technical issues associated with the development of recommended exposure limits. Special emphasis will be placed on discussion of the following:

(1) What animal and human data best describe the health concerns from exposure to titanium dioxide?

(2) What strategies are being used to control occupational exposure to titanium dioxide (*e.g.,* engineering controls, work practices, personal protective equipment)?

(3) At what workplaces and occupations can exposure to titanium dioxide occur?

(4) What challenges exist in measuring workplace exposures to titanium dioxide?

(5) What are areas of future collaborative efforts (*e.g.,* research, communication, development of exposure measurement and control strategies)?

The public is invited to attend and will have the opportunity to provide comments.

Summary: NIOSH currently recommends that titanium dioxide be considered a potential occupational carcinogen. A review of the recent literature indicates that the NIOSH recommendation may not adequately reflect current scientific information about the potential biological activity of titanium dioxide and other similar substances that have poor solubility and can occur in the workplace. Recent evidence suggests that these substances, which generally have been regarded as causing minimal toxicity in humans, may pose different levels of risk depending on their particle size. Ultrafine particles appear to be more toxic than an equivalent mass dose of larger respirable particles, an effect that appears to be related to the total particle surface area. Moreover, when the exposure-response data are evaluated from studies in rats exposed to titanium dioxide and other similar substances, there appears to be a consistent response that is related to particle surface area. NIOSH presently is reviewing the available toxicity data on titanium dioxide, as well as other relevant health data associated with particle surface area, with the intent of developing new workplace recommendations for titanium dioxide, including recommended exposure limits (RELs).

NIOSH seeks to obtain materials, including published and unpublished reports and research findings, to evaluate the possible health risks of occupational exposure to titanium dioxide (including particle size-specific information). Examples of requested information include, but are not to be limited to, the following:

(1) Identification of industries or occupations in which exposures to titanium dioxide may occur.

(2) Trends in the production and use of titanium dioxide.

(3) Description of work tasks and scenarios with a potential for exposure to titanium dioxide.

(4) Current and historical exposure measurement data in various types of industries and jobs.

(5) Case reports or other health information demonstrating health effects in workers exposed to titanium dioxide.

(6) Reports of experimental in vivo and in vitro studies that provide evidence of a dose-relationship between the particle size of a substance and its biological activity.

(7) Reports of experimental inhalation studies with rodents demonstrating a relationship between the particle size or surface area of a substance and lung inflammation, fibrosis, and biochemical mediators.

(8) Description of work practices and engineering controls used to reduce or prevent workplace exposure to titanium dioxide.

(9) Educational materials for worker safety and training on the safe handling of titanium dioxide.

(10) Data pertaining to the feasibility of establishing particle size-specific RELs for titanium dioxide.

NIOSH will use this information to determine the need for developing new recommendations for reducing occupational exposure to titanium dioxide.

ADDRESSES: Comments should be submitted to the NIOSH Docket Office, ATTN: Diane Miller, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226, telephone 513/533–8450, fax 513/533–8230. Comments may also be submitted by email to: *niocindocket@cdc.gov.* Email attachments should be formatted as Microsoft Word. Comments should be submitted to NIOSH no later than April 16, 2004, and should reference docket number NIOSH–033 in the subject heading.

All information received in response to this notice will be available for public examination and copying at the NIOSH Docket Office, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

Contact Persons for Technical Information: Eileen Kuempel, M/S C–15, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226, 513/533–8363, or Ralph Zumwalde, M/S C–32, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226, 513/533–8320.

The Director, Management Analysis and Services Office, has been delegated the authority to sign **Federal Register** Notices pertaining to announcements of meetings and other committee management activities, for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: March 9, 2004.

Alvin Hall,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. 04–5855 Filed 3–15–04; 8:45 am]

BILLING CODE 4163–19–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2000N–1449]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Changes to an Approved New Drug Application or Abbreviated New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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

DATES: Fax written comments on the collection of information by April 15, 2004.

ADDRESSES: OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. 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: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Management Programs (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.

Changes to an Approved New Drug Application or Abbreviated New Drug Application—(OMB Control Number 0910–0431)—Extension

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (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 new drug applications (NDAs) and abbreviated new drug applications (ANDAs), to new and abbreviated animal drug applications, and to license applications for biological products.

The guidance is intended to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 116 of 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.

The guidance provides recommendations to holders of approved NDAs and ANDAs 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 these areas: (1) Components and composition, (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7) miscellaneous changes.

Some of the basic elements of section 506A of the act are as follows:

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.

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).

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 the following possibilities: (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).

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).

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.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Federal Food, Drug, and Cosmetic Act Section	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
506A(c)(1) and (c)(2)—Prior Approval Supplement	263	5.8	1,517	150	227,550
506A(d)(1)(B),(d)(1)(C), and (d)(3)(B)(i)—Changes being effected (CBE) in 30-days Supplement	274	8.5	2,322	95	220,590
506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(ii)—CBE Supplement	202	9.7	1,959	95	186,105
506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B)—Annual Report	580	13.2	7,639	35	267,365
Total					901,610

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

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, and 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 these sections of the act, 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 1,517 supplements will be submitted annually under section 506A(c)(1) and (c)(2) of the act. FDA estimates that approximately 263 applicants will submit such supplements, and that it will take approximately 150 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i) 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 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 2,322 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 274 applicants will submit such supplements, and that it will take approximately 95 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 1,959 supplements will be submitted annually under section 506A(d)(3)(B)(ii) of the act. FDA estimates that approximately 202 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(A), (d)(1)(C), (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 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 7,639 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). FDA estimates that approximately 580 applicants will submit such information and that it will take approximately 35 hours to prepare and submit to FDA the information for each annual report.

In the **Federal Register** of December 19, 2003 (68 FR 70813), FDA published a 60-day notice requesting public comment on the information collection

provisions. One comment was received. The comment did not specifically address the information collection burden estimates. The comment stated that parenteral drug products do not have postapproval change guidance documents, and that this has caused the company to evaluate changes from a very conservative viewpoint, resulting in a high number of man-hours involved in the assembly and submission of postapproval changes. The comment recommended the incorporation of risk-based analysis.

FDA response: The recommendations provided in the guidance have significantly lowered the filing requirements for postapproval changes to parenteral drug products. For example, under 21 CFR 314.70(b)(2)(v), a change to the method of manufacture of a drug product required a prior approval supplement. Under the guidance, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product (section VII.C.2.a of the guidance *at http://www.fda.gov/cder/guidance/2766fnl.htm#1*) would be submitted as a changes-being-effected supplement. The agency is continuing to work to further address filing requirements for postapproval changes of parenteral drug products.

Dated: March 9, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–5832 Filed 3–15–04; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004N–0101]

Agency Information Collection Activities; Proposed Collection; Comment Request; Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents; and Requirements for Donor Notification

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the information collection requirements relating to requirements for testing human blood donors for evidence of infection due to communicable disease agents and for donor notification.

DATES: Submit written or electronic comments on the collection of information by May 17, 2004.

ADDRESSES: Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. All comments should be identified with the docket number found in brackets in the heading of this document. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: JonnaLynn P. Capezzuto, Office of Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following 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.

Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents; and Requirements for Donor Notification (OMB Control Number 0910–0472)—Extension

Under sections 351 and 361 of the Public Health Service Act (PHS Act)(42 U.S.C. 262 and 264) and the provisions of the Federal Food, Drug, and Cosmetic Act (the act) that apply to drugs (21 U.S.C. 321 *et seq.*), FDA may issue and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between States or Possessions or from foreign countries into the States or Possessions. The public health objective in testing human blood donors for evidence of infection due to communicable disease agents and in donor notification is to prevent the transmission of communicable disease. Section 351 of the PHS Act, applies to biological products. Blood and blood components are considered drugs, as that term is defined in section 201(g)(1) of the act (21 U.S.C. 321(g)(1)).

Section 610.40(c)(1)(ii) (§ 610.40(c)(1)(ii) requires each dedicated donation be labeled, as required under § 606.121 (21 CFR 606.121), and with a label entitled ''INTENDED RECIPIENT INFORMATION LABEL'' containing the name and identifying information of the recipient. (21 CFR 606.121 is approved under OMB control number 0910–0116.) Section 610.40(g)(2) requires an establishment to obtain written approval from FDA to ship human blood or blood components for further manufacturing use prior to completion of testing. Section 610.40(h)(2)(ii)(A) requires an establishment to obtain written approval from FDA to use or ship human blood or blood components found to be reactive by a screening test for evidence of a communicable disease agent(s) or collect from a donor with a record of a reactive screening test. Sections 610.40(h)(2)(ii)(C) and (h)(2)(ii)(D) require an establishment to label reactive human blood and blood components with the appropriate screening test results, and, if they are intended for further manufacturing use into injectable products, with a statement indicating the exempted use specifically approved by FDA. Section 610.40(h)(2)(vi) requires each donation of human blood or blood component that tests reactive by a screening test for syphilis and is determined to be a