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.


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.


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,
Programs (HFA
Karen L. Nelson, Office of Management
FOR FURTHER INFORMATION CONTACT:
OMB, Attn: Fumie Yokota, Desk Officer
12332 Federal Register
Application or Abbreviated New Drug
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)(ii) 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
currently may 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

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, the applicant must submit a supplement to FDA before distributing a drug 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 supplements will be submitted annually under section 506A(d)(3)(B)(i) of the act. 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)—CBE Supplement 274 8.5 1,959 95 186,105

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

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

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


Jeffrey Shuren,
Assistant Commissioner for Policy.

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

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 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(1) 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 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