DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 5, 25, 500, 510, 514, and 558

[Docket No. 99N–1415]

RIN 0910–AB49

Supplements and Other Changes to Approved New Animal Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations on supplements and other changes to an approved new animal drug application (NADA) or abbreviated new animal drug application (ANADA) to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). This proposed rule would require manufacturers to validate the effect of any manufacturing change on the identity, strength, quality, purity, and potency of a new animal drug as those factors relate to the safety or effectiveness of the product. The proposal identifies changes requiring submission and approval of a supplement prior to the distribution of the new animal drug made using the change, changes requiring the submission of a supplement at least 30 days prior to the distribution of the new animal drug, changes requiring the submission of a supplement at the time of distribution, and changes to be described in an annual report.

DATES: Written comments by December 15, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (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: Dennis M. Bensley, Jr., Center for Veterinary Medicine (HFV–140), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6956.

SUPPLEMENTARY INFORMATION:

I. Introduction

On November 21, 1997, the President signed the Modernization Act into law (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 NADA's and ANADA's, new drug applications (NDA's) and abbreviated new drug applications (ANDA's), and to license applications for biological products. This proposed rule sets forth regulations to implement section 506A of the act for NADA's and ANADA's. The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) are issuing separate proposed regulations regarding manufacturing changes for NDA's and ANDA's and for licensed biological products.

Section 506A of the act makes no distinction between the requirements for reporting manufacturing changes for human drug and biological products regulated by CDER and CBER and for new animal drug products regulated by the Center for Veterinary Medicine (CVM). CVM is proposing this rule to harmonize the reporting requirements of manufacturing changes for new animal drug products with those reporting requirements for human drug and biological products.

The Modernization Act, section 116, becomes effective on the effective date of these final regulations or 24 months after the enactment of the Modernization Act (November 21, 1999), whichever occurs first. This proposed rule updates and will replace § 514.8 (21 CFR 514.8), which provides the current requirements for manufacturing changes for NADA's.

II. Background

A. CVM's Current Rule

CVM currently evaluates all manufacturing changes to approved NADA's under the regulations found in § 514.8. Manufacturing changes are currently submitted as permitted changes (§ 514.8(a)(5)), changes being effected (CBE's) (§ 514.8(d), or changes requiring approval prior to implementation (§ 514.8(a)(4)).

Under current § 514.8(a)(5), permitted changes may be put into effect without the approval of a supplemental application but must be reported in the next annual drug experience report (DER). Section 514.8(a)(5) lists the types of manufacturing changes that are considered permitted changes.

CBE's under current § 514.8(d) include manufacturing changes that would ''give increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess.'' Such changes are to be placed into effect at the earliest possible time with concurrent submission of a supplemental application; hence such changes do not require CVM approval before implementation.

Changes requiring approval of a supplemental application prior to implementation are set out in current § 514.8(a)(4) of the regulations. Most manufacturing changes are currently reported in preapproval supplemental applications under § 514.8(a)(4).

B. Section 116 of The Modernization Act

Many of the concepts included in the Modernization Act were incorporated from earlier rulemaking and guidance documents issued by CDER and CBER. A discussion of CDER's earlier rulemaking, guidance documents, and their underlying rationale can be found in the preamble to CDER's proposed rulemaking to comply with section 506A of the act.

CDER had issued a series of guidance documents to ease preapproval requirements for certain manufacturing changes that are unlikely to have a detectable impact on a drug product's quality and performance as distinguished from those that could have a significant impact. These guidance documents were issued under a provision in current 21 CFR 314.70(a) that permits holders of an approved application to make changes to the application in accordance with a guideline, notice, or regulation published in the **Federal Register** that provides a less burdensome notification of the change.

As of this date, CDER has issued several guidances addressing the requirements relating to postapproval changes in manufacturing and controls. These are known as the SUPAC (Scale-Up and Postapproval Changes) documents. The first of these guidance documents was published in November 1995 and is entitled ''Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Dissolution Testing; *In Vivo* Bioequivalence Documentation'' (SUPAC–IR). This guidance provides recommendations to holders of approved drug applications who intend, during the postapproval period, to change: (1) The components or composition, (2) the site of manufacture, (3) the scale of manufacture, and/or (4)

the manufacturing (process and/or equipment) of an immediate release solid oral dosage form.

In May 1997 and August 1997, CDER issued two related guidances entitled ''Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Release Testing; *In Vivo* Bioequivalence Documentation'' (SUPAC–SS) and ''Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: *In Vitro* Dissolution Testing; *In Vivo* Bioequivalence Documentation'' (SUPAC–MR). These two guidances cover the same general topics and use the same general approaches as SUPAC–IR. The current series of guidance documents relating to scale-up and postapproval changes focuses on changes to manufacturing and controls for drug products. Future guidances will consider changes in manufacturing and controls for the drug substance, product containers and closures, and other topics as well.

The underlying rationale of these guidances already completed or in preparation is that the identity, strength, quality, purity, and potency of an approved drug should remain unchanged in any important aspect as a result of any postapproval change in manufacturing and controls. This unchanged performance extends to changes that might affect in vivo bioavailability and relative bioavailability (bioequivalence).

CDER's guidance documents, described previously, originally applied only to drug products approved under sections 505 (new and abbreviated new drug applications) and 507 (antibiotic applications; revoked by the Modernization Act) of the act (21 U.S.C. 355 and 357). However, CVM adopted many of the concepts described in these guidance documents by permitting the reporting of minor manufacturing changes in a biennial supplement instead of in a preapproval supplement submitted in accordance with the current regulation (§ 514.8). The biennial supplement does not require CVM approval prior to the distribution of the drug product made using the changes.

CDER's and CBER's proposed rulemaking and supporting guidance documents allow for many moderate manufacturing changes to be reported as CBE's that are not provided for in CVM's current regulations (§ 514.8). CVM is proposing regulations that harmonize the reporting of manufacturing changes for new animal drug products with the reporting of manufacturing changes for human drug products, because: (1) The act makes no distinction between the requirements for the reporting of manufacturing changes for human drug products and for new animal drug products, (2) the act does not provide for the reporting of minor manufacturing changes in biennial supplements, (3) the proposed rulemaking allows for flexibility in reporting many moderate changes as CBE's, and (4) CVM and the animal drug industry can benefit from CDER's expertise and resources to issue specific guidances on manufacturing and controls changes used for drugs, generally.

CVM is currently collaborating with CDER on a number of guidance documents addressing manufacturing and controls changes, including the draft guidance document entitled ''Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA'' to be made available for comment along with this proposed rulemaking. On the effective date of these final regulations or on November 21, 1999, whichever occurs first, CVM's previous practices will be superseded by section 506A of the act and/or the final regulations and the reporting of minor manufacturing changes in biennial supplements will no longer be permitted. CVM proposes to adopt CDER's current guidance documents for manufacturing changes (SUPAC–IR, SUPAC–SS and SUPAC–MR). These documents will be updated to reflect changes resulting from the proposed rulemaking, and CVM intends to participate with CDER in the drafting of any guidance documents covering manufacturing changes. In addition, CVM will also issue guidance documents for specific new animal drug products such as Type A medicated articles.

III. Summary of the Legislation

Section 116 of the Modernization Act amended the act by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug made with such changes. Section 506A of the act 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 and 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 that FDA deems appropriate and include the information developed by the applicant validating the effects of the change (section 506A(c)(1) of the act). The phrase ''validating the effects of the change,'' as used in this proposed rule, is not the same as ''validation'' required in FDA's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211).

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 regulation or guidance, (2) a change determined by FDA through regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change or a reference listed drug, and (3) other changes determined 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 establish categories of manufacturing changes, other than major manufacturing changes, and require submission of a supplemental application for drugs made with such manufacturing changes (section 506A(d)(1)(B) and (d)(1)(C) of the act). For changes, other than major changes, that require submission of a supplemental application, the applicant may begin distribution of the drug 30 days after FDA receives the supplemental application unless the agency notifies the applicant within the 30-day period that FDA review and 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 for which the applicant may begin distributing a drug made with such changes upon receipt by the agency of the supplemental application for the change (section 506A(d)(3)(B)(ii) of the act). If FDA fails

to approve 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 a reporting requirement, the act permits FDA to authorize the applicant to submit a single annual report containing the required information for all the changes made during the year (section 506A(d)(2)(B) of the act).

Section 506A of the act recognizes that the amount of testing and the data to be included in a submission and the appropriate method for reporting the data are related to the scope and the type of change being made. Four methods of reporting changes (i.e., supplements that require FDA review and prior approval, CBE's supplements with a 30-day wait, CBE's supplements with no wait, and annual reports) are discussed in section 506A of the act and in this proposal. The appropriate method for reporting any specific change depends on the potential for that change to impact the fundamental safety or effectiveness of the product by adversely affecting the basic aspects of the drug product—its identity, strength, quality, purity, and potency.

The main objective of a review of a supplemental application that documents postapproval changes to an NADA or ANADA is to ensure ''sameness'' or ''equivalence'' between the pre- and post-change product. ''Sameness or equivalence'' do not mean ''identical'' since certain manufacturing changes lead to differences. Such differences should not, however, affect the safety or effectiveness of the drug product. Also, a proposed manufacturing change should not be so extensive that a new drug product is created. If a manufacturing change does produce a fundamental alteration (i.e., a pharmaceutically inequivalent dose form), a new application may be required for the resulting product.

Generally, in the case of NADA products, the pre- and post-change drug product should be compared. In the case of ANADA products, the pre- and post-change drug products should be compared to the reference listed drug, typically the pioneer drug product. Confirmation of ''sameness'' or ''equivalence'' is particularly important when changes are made that involve the active pharmaceutical ingredient or affect critical manufacturing steps. Examples of such changes include, but are not limited to, components and overall composition of the formulation; manufacturing site, scale, equipment, process, or specifications; and analytical procedures.

Many factors should be considered in determining whether a change has a substantial, moderate, or minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Some types of manufacturing changes have a greater potential to cause unwanted or unexpected changes to the product that may be difficult to assess by merely testing to specifications. The type of product is also a factor to consider in determining the potential risk of a manufacturing change having an adverse effect on the product. Some products may be substantially affected by what appear to be small manufacturing changes.

Therefore, defining ''substantial,'' ''moderate,'' and ''minimal'' in the regulations with such specificity that they exhaustively describe all of the many individual changes that may occur is not feasible. FDA is planning, however, to provide greater detail in guidance about the types or categories of changes that the agency believes should be considered ''substantial,'' ''moderate,'' or ''minimal.''

Section 506A of the act provides FDA with considerable flexibility to establish required information and filing requirements for manufacturing changes. There is a corresponding need to retain such flexibility in the proposed regulations implementing section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility is necessary to be responsive to increasing knowledge of and experience with certain types of changes and to help ensure the effectiveness 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 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 agency believes it can more readily respond to knowledge gained from manufacturing experience, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories. The proposed rule would, therefore, reduce the number of manufacturing changes specifically identified as being subject to supplements requiring or not requiring review and approval. The agency also understands that applicants expect some predictability on what type of reporting will be expected for specific changes. FDA intends to make available guidance documents to describe the agency's current interpretation of specific changes falling into the four filing categories and to modify the documents as needed to reflect changes based on new information. The use of guidance documents as provided for in section 506A of the act will allow FDA to more easily and quickly modify and update important information. Guidance documents will be developed according to the procedures set out in FDA's Good Guidance Practices as published in the **Federal Register** of February 27, 1997 (62 FR 8961 at 8967 to 8972). A notice of availability for a draft guidance entitled ''Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA'' is published elsewhere in this issue of the **Federal Register**. This guidance covers recommended reporting categories for various postapproval manufacturing changes. FDA has published guidances, including SUPAC guidances and CVM's ''Animal Drug Manufacturing Guidelines,'' that provide recommendations on both reporting categories and/or the type of information that should be developed by the applicant to validate the effect of the change on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product. To the extent that the recommendations on reporting categories in this proposed guidance, when finalized, are

inconsistent with previously published guidances, such as the SUPAC's, the recommended reporting categories in such prior guidances will be superseded by this new guidance upon its publication in final form. FDA intends to update the prior published guidances to make them consistent with this guidance.

IV. Description of the Proposed Rule

A. Definitions

FDA has added a new paragraph to define terms and phrases as used in proposed § 514.8. Proposed § 514.8(a) would add definitions of ''minor changes and stability report (MCSR),'' ''specification,'' ''validate the effects of the change,'' 'listed drug,'' and ''the list.'' These definitions are necessary to implement the provisions of section 506A of the act.

FDA is proposing to define ''specification'' as the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process controls. FDA is proposing to define ''specification'' because section 506A of the act includes a change ''in the specifications in the approved application or license'' as a major change. To clarify the meaning of the term ''acceptance criteria'' as used in the definition of ''specification,'' FDA is including in the proposed definition of ''specification'' the statement that ''acceptance criteria'' refers to numerical limits, ranges, or other criteria for the tests described. To determine if a material being tested complies with a specification, there must be predetermined criteria. These criteria may include numerical limits or ranges (e.g., not more than 1 percent) or other criteria (e.g., white to off-white in color).

FDA is proposing to define the phrase ''validate the effects of the change'' as an assessment of the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug. FDA is proposing to define this phrase because section 506A of the act includes a requirement that a drug made with a manufacturing change may only be distributed after the applicant validates the effects of the change. Validating the effects of the change is important in determining whether manufacturing changes alter the identity, strength, quality, purity, or potency of a drug product as these factors may relate to drug safety or effectiveness, and includes testing beyond that in an approved specification, such as redocumentation of the pharmaceutical equivalence or bioequivalence.

''Minor changes and stability report'' would mean a report that is submitted once each year within 60 days of the anniversary of the application's original approval or a mutually agreed upon date for minor manufacturing changes made according to proposed § 514.8(b)(4) or a statement that no changes were made, and updated stability data generated on commercial or production batches according to an approved stability protocol.

The MCSR is the annual report described in section 506A(d)(2)(B) of the act, and it is different and distinct from the annual report described and submitted in accordance with current § 510.300 (21 CFR 510.300) (i.e., periodic DER's). The MCSR is a type of ''annual'' report for manufacturing changes only. The MCSR would be submitted to and reviewed by CVM's Office of New Animal Drug Evaluation (ONADE) rather than by CVM's Office of Surveillance and Compliance (OSC). The MCSR must include minor manufacturing changes implemented over the past year and an update of ongoing stability data generated on production lots. Currently, ongoing stability data are submitted as part of DER's to OSC. CVM has decided that it is more efficient to allow the administrative review of information relating to manufacturing changes and stability to reside in one group. Information regarding labeling changes and product defects would continue to be submitted to CVM's OSC.

FDA is proposing to define ''listed drug'' and ''the list'' to clarify ''reference listed drug'' cited in proposed § 514.8(b)(2)(ii)(B).

B. Manufacturing Changes to an Approved Application

Proposed § 514.8(b) sets forth general requirements under which an applicant must notify FDA when making a change to an approved application and replaces current § 514.8(a). This paragraph states that an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, and that the notice is required to describe the change fully. It also states that the applicant must, depending on the type of change, notify FDA of the change in a supplement under proposed § 514.8(b)(2) or (b)(3) or by the inclusion of the information in an annual report (the MCSR) under proposed § 514.8(b)(4). Reference in current § 514.8(a)(1) to current regulations, § 510.300, has been deleted and, instead, proposed § 514.8(b)(1)(i) makes reference to annual reports described under proposed § 514.8(b)(4). Manufacturing changes and/or updated stability data generated according to an approved stability commitment would no longer be reported in periodic DER's (i.e., annual reports under current § 510.300) but be reported under proposed § 514.8(b)(4) in an MCSR. CVM intends to publish a final rule revising § 510.300, which will be renumbered as § 514.80. Since CVM expects to publish the final rule for § 514.80 (*Records and reports concerning experience with new animal drugs for which an approved application is in effect.* (56 FR 65581, December 17, 1991)) before the final rule for § 514.8, CVM will, if necessary, amend the rule for *Records and reports concerning experience with new animal drugs for which an approved application is in effect.* after the final rule for § 514.8 publishes.

Proposed § 514.8(b)(1)(ii) would require the holder of an approved application under section 512 of the act (21 U.S.C. 360b) to validate the effects of manufacturing changes on the identity, strength (e.g., assay and content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products) and potency (e.g., biological activity, bioavailability, and bioequivalence) of a drug as these factors may relate to the safety or effectiveness of the drug. These validation requirements must be met before a product made with a manufacturing change may be distributed. This amendment implements section 506A(a)(1) and (b) of the act.

Proposed § 514.8(b)(1)(iii) states that notwithstanding the requirements of § 514.8(b)(2) and (b)(3), an applicant must report a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change. For example, a type of manufacturing change subject to review and approval by FDA under proposed § 514.8(b)(2) might be identified in regulation or guidance as a change that could be reported in a supplement not requiring review and approval or in an annual report. CDER used this provision to reduce the regulatory burden for submission of supplements for manufacturing changes that were not likely to adversely affect drug product quality or performance in the SUPAC guidance documents.

Proposed § 514.8(b)(1)(iv) requires the applicant to include in each supplemental application providing for a change under proposed § 514.8(b)(2) or (b)(3), a statement that a copy of the supplement has been provided to the appropriate FDA district office whose jurisdiction includes the facility where the manufacturing change is implemented.

Proposed § 514.8(b)(1)(v) would add a requirement that a list of all changes contained in the supplement or annual report must be included in the cover letter for the supplement or annual report. For many years, most supplements and annual reports have routinely included such cover letters. Including a list of all changes in the cover letters will enable FDA to more efficiently locate and evaluate changes in what are often substantial documents, thus facilitating FDA review of supplements and annual reports.

Proposed § 514.8(b)(2)(iii) describes the information that must be included in a supplement. References to regulations for categorical exclusion or an environmental assessment have been updated and included in § 514.8(b)(2)(iii)(K).

C. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Change)

Certain drug manufacturing steps are so critical that changes in these steps must be subject to the submission of a supplement to FDA that is approved by FDA prior to distribution of the drug product made using the change. Current § 514.8(a)(4) sets forth changes for which such review and approval are required.

Proposed § 514.8(b)(2) would revise the current sections to implement section 506A of the act. Proposed § 514.8(b)(2)(i) implements section 506A(c)(2) of the act and would require a preapproval supplement to be submitted for any major change, i.e., 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.

Also, there are times when manufacturing changes are demonstrated to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases the applicant chooses not to implement these manufacturing changes, but in other cases the applicant may still wish to do so. If an assessment by the sponsor shows that a manufacturing change has adversely affected the identity, strength, quality, purity, or potency of the drug product and the sponsor wants to make the change, the change should be filed in a supplement that requires review and approval by FDA before distribution of the product, regardless of whether the change is listed as an example of one that normally does not need FDA approval prior to distribution of the product made with the change. The applicant should submit this change in a supplement that requires review and approval with appropriate information to demonstrate that the manufacturing change has not altered the continued safety and effectiveness of the product. The agency will assess the effect of any adverse change in a drug product, as the change may relate to the safety or effectiveness of the product, during the review of the supplement that requires approval prior to distribution of the product.

Proposed § 514.8(b)(2)(ii) lists examples of those changes requiring submission and approval of a supplement prior to distribution, including those designated as major manufacturing changes in section 506A(c)(2) of the act, and changes to certain biotechnology products. These changes have 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 agency's continued review and approval of these changes prior to product distribution is necessary to protect the animals and the public from products for which safety or effectiveness may have been compromised.

FDA is proposing to describe additional specific examples of changes that have substantial, moderate, and minimal potential to adversely affect a product in guidance documents rather than enumerate them in the proposed regulations. As discussed previously, section 506A of the act expressly states that the agency, through guidance, may categorize the manufacturing changes. FDA anticipates that scientific advances and future experience may reduce the need for approval of supplements providing for certain changes, and the agency will respond to changed circumstances by revising the guidance documents. A notice of availability of a draft guidance document entitled ''Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA,'' that provides more detailed recommendations on how to report proposed changes, is being published elsewhere in this issue of the **Federal Register**, and the agency is soliciting comments on the draft guidance in addition to the proposed rule.

In regard to proposed § 514.8(b)(2)(ii)(B), section 506A of the act also states in part that ''* * * equivalence of the drug to the drug as manufactured without the change'' should be demonstrated. For those generic drug products for which, at the time of approval, a generic drug applicant was required to show equivalence between the proposed generic drug and a reference listed drug (typically the referenced pioneer drug product), a proposed manufacturing change should not significantly change the equivalence demonstrated at the time of approval. In addition, for the more significant manufacturing changes for generic drugs the approval of which relied on a demonstration of bioequivalence to a reference listed drug, the applicant is required to conduct a bioequivalence study comparing the drug product made with the change to the reference listed drug, typically the pioneer drug product.

Under proposed § 514.8 (b)(2)(ii)(G) changes to a product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting the application require approval prior to distribution. Until questions about the integrity of the data in the application have been resolved, there are inadequate assurances that any change will not adversely affect the safety or effectiveness of the product. Moreover, a change to a product cannot be validated, as required under 506A(b) of the act, until the integrity of the underlying data in such an application is validated. Consequently, there is a significant potential that the change will have an adverse effect on the identity, strength, quality, purity, or potency of the product. After a validity assessment has been completed, and data integrity questions resolved, the holder of an approved application may submit supplements for manufacturing changes as otherwise provided in § 514.8.

Current § 514.8(a)(4)(iii), (a)(4)(iv), and (a)(4)(v) regarding general manufacturing and control changes requiring approval prior to distribution are not included in proposed § 514.8(b)(2), because some of these changes would fall into the proposed major manufacturing change category while others would fall into other proposed categories depending on whether the change is considered to have a substantial, moderate, or minimal potential to adversely affect the

identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of the drug. FDA plans to provide recommendations on how to submit the supplements in guidance documents, including the draft guidance document mentioned previously. Current § 514.8(a)(4)(v) relating to identification of distributors has been updated and reproposed as § 514.8(c)(4).

Proposed § 514.8(b)(2)(iii) states that the applicant must obtain approval of a supplement from FDA before distributing a product using a change under § 514.8(b)(2), and it specifies information to be included in the supplement.

Proposed § 514.8(b)(2)(iv) permits a request for an expedited review of a supplement for public health reasons or if a delay in making the change described in the supplement would impose an extraordinary hardship on the applicant. FDA is including this provision for expedited review for extraordinary hardship reasons but wishes to clarify that these requests should focus on manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan. Requests for expedited review will be assessed on a case-by-case basis. All requests may not be granted.

Under proposed § 514.8(b)(2)(v), an applicant may submit one or more protocols describing specific tests, validation studies, and acceptable limits to be achieved to demonstrate the lack of an adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such protocols, or changes to a protocol, would be submitted as a supplement requiring approval from FDA prior to distribution. If approved, the use of such a protocol in making the specified changes may justify a reduced reporting category for the change because of the reduced risk of an adverse effect.

Generally, when considering a change in the manufacture of a product, the manufacturer will prepare a protocol, often called a ''comparability protocol,'' identifying tests to be performed in evaluating the change and its effect on the product and defining the criteria against which the impact of the change will be evaluated. By providing FDA an opportunity to review and approve the comparability protocol before it is used by the applicant to evaluate a change, FDA can have a greater assurance that the change is being properly evaluated and there is, therefore, less potential for the change to have an adverse effect on the safety or effectiveness of the product.

D. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

Current § 514.8(d)(3) provides for manufacturing changes that give an increased assurance that the drug will have the characteristics of identity, strength, quality, and purity that it purports or is represented to possess to be placed into effect at the earliest possible time. Proposed § 514.8(b)(3) implements section 506A(d)(1)(B) and (d)(3) of the act and provides that products made using the changes listed under this section may only be distributed not sooner than 30 days after receipt of a supplement by FDA. FDA recognizes that animal and the public health can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so that there is a mechanism for assessing the consequences of the change and that the agency approve such changes. The requirement to submit a supplement 30 days before distribution of the product balances FDA's need to review applications to protect against the distribution of unsafe or ineffective products and the need to make improved products available.

Proposed § 514.8(b)(3)(i) would require that a supplement 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. Proposed § 514.8(b)(3)(iii) states that a supplement submitted under § 514.8(b)(3)(i) is required to give a full explanation of the basis for the change and identify the date on which the change is to be made, and that the supplement must be labeled ''Supplement—Changes Being Effected in 30 Days.''

Proposed § 514.8(b)(3)(ii) describes the types of changes that require submission of a supplement 30 days before distribution.

Proposed § 514.8(b)(3)(iv) states that distribution of a product made using a change listed under this section may not begin until 30 days after receipt of a supplement by FDA. This section would also require that the same information listed in proposed § 514.8(b)(2)(iii), discussed previously, must be contained in the supplement required under proposed § 514.8(b)(3).

According to proposed § 514.8(b)(3)(v), during the 30-day period following receipt of the supplement, FDA would perform a preliminary review to determine whether the supplement is complete and whether the type of change is appropriate for review as a supplement under proposed § 514.8(b)(3). If the proposed change is determined to be a major change that should appropriately be submitted under proposed § 514.8(b)(2), the agency would inform the applicant and the applicant would be required to receive FDA's approval before a product produced with the change could be distributed. If FDA determines that the change is properly submitted as a supplement under § 514.8(b)(3)(i), but the required information is incomplete, the applicant would be required to supply the missing information and wait until FDA has determined that the supplement is in compliance before distributing the product.

Under proposed § 514.8(b)(3)(vii), if FDA disapproves a supplemental application under this section, the agency may order the manufacturer to cease distribution of the drug products made with the manufacturing change. This amendment would implement section 506A(d)(3)(B)(iii) of the act.

E. Changes That May Be Implemented When FDA Receives a Supplement (Moderate Changes)

Section 506A(d)(3)(B)(ii) of the act gives FDA authority to designate a category of changes for which the holder of an approved application making such change may begin distribution of the drug upon receipt by FDA of a supplemental application for the change. FDA recognizes that animals and the public can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so that there is a mechanism for assessing the consequences of the change and that the agency approve such changes. However, based on FDA's experience, certain changes may be implemented when FDA receives the supplement, rather than delaying distribution for 30 days because, in general, these changes provide the same or increased assurance that the product will have the characteristics of identity, strength,

quality, purity, or potency that it purports or is represented to have. Submission of a supplement gives FDA ready access to information regarding such changes. The requirement for approval of such supplements allows FDA to protect against the distribution of unsafe or ineffective products while allowing products that are likely to be improved to be available more quickly. Examples of such changes are listed in proposed § 514.8(b)(3)(vi). The supplement submitted under this paragraph is required to give a full explanation of the basis for the change and the supplement must be labeled ''Supplement—Changes Being Effected.''

Under proposed § 514.8(b)(3)(vii), if FDA disapproves a supplemental application under this section, the agency may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

Current § 514.8(d) describes the types of changes that can be placed into effect at the earliest possible time. Such changes are being described in proposed § 514.8(b)(3)(vi) and (c)(3).

F. Changes and Updated Stability Data to Be Described and Submitted in an Annual Report (Minor Changes)

Minor manufacturing changes are currently submitted in an annual report under § 510.300(b)(6) as referenced in current § 514.8(a)(5) or in a biennial supplement. Proposed § 514.8(b)(4) would provide that changes to 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 as these factors may relate to the safety or effectiveness of the product be documented by the applicant in the next annual report, i.e., ''Minor Changes and Stability Report,'' as described under proposed § 514.8(b)(4). FDA recognizes that there are manufacturing changes that have a minimal potential to have an adverse affect on a product's safety or effectiveness. FDA believes that agency approval of these changes prior to product distribution is unnecessary and is proposing in § 514.8(b)(4) that such changes would not be required to be approved by the agency. FDA continues to believe that it is important that such changes be documented and validated so that FDA can assess the consequences of the change. FDA can effectively assess compliance with this section and CGMP requirements for changes that have a minimal potential to adversely affect the product's safety or effectiveness by having ready access to information regarding such changes through submission of an annual report and by inspection.

Section 506A(d)(1)(C) of the act authorizes FDA to establish reporting categories (i.e., annual report) of manufacturing changes (i.e., minor changes) that may be made without submitting a supplemental application. Section 506A(d)(2)(A) of the act permits minor changes to be reported separately or in an annual report. Section 506A of the act has no provisions for reporting minor manufacturing changes in biennial supplements as permitted by CVM's pilot program. Therefore, all minor manufacturing changes described in regulations or guidance should be submitted in an MCSR to the application annually. The MCSR will be reviewed by the appropriate CVM office that reviews manufacturing supplements. No manufacturing changes or updated stability data are to be reported in the periodic DER that is submitted to CVM's OSC. But reports of manufacturing defects must continue to be submitted to OSC. The MCSR must be submitted each year within 60 days of the anniversary of approval of the application or mutually agreed upon date. Proposed § 514.8(b)(4)(ii) lists examples of changes that can be reported in the MCSR.

Proposed § 514.8(b)(4)(iii) states that the MCSR must list all products to which minor changes were made.

Proposed § 514.8(b)(4) replaces current § 514.8(a)(5).

G. Labeling and Other Changes Requiring Submission and Approval of a Supplement Prior to Distribution of the Product Made Using the Change (Major Changes)

Labeling changes addressed in current § 514.8(a) and (b) are newly addressed by proposed § 514.8(c). Proposed § 514.8(c)(1) describes when an applicant must notify FDA that the applicant is making such a change to an approved application. This section states that an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, and that the notice is required to describe the change fully.

Proposed § 514.8(c)(2) updates current § 514.8(a)(3), (a)(4)(i) and (a)(4)(ii) regarding labeling changes and addition of intended use requiring preapproval supplements. Labeling and other changes requiring submission of a supplemental application are described in proposed § 514.8(c)(2)(i).

Proposed § 514.8(c)(2)(ii) requires an applicant to obtain approval of a supplement by FDA before distributing a product subject to a change listed under § 514.8(c)(2)(i), and specifies information to be included in the supplement.

Current § 514.8(a)(3) regarding mailing or promotional pieces for a prescription drug has been updated and is included under proposed § 514.8(c)(2). Current § 514.8(a)(4)(i) and (a)(4)(ii) regarding revisions in labeling and addition of claim, respectively, have been updated and included under proposed § 514.8(c)(2)(i)(A) and (c)(2)(i)(B).

H. Labeling Changes To Be Placed Into Effect Prior to Receipt of a Written Notice of Approval of a Supplemental Application

Proposed § 514.8(c)(3) updates and redesignates current § 514.8(d) regarding labeling changes to be placed into effect prior to receipt of a written notice of approval of a supplemental application.

Proposed § 514.8(c)(3)(i) requires labeling changes that increase the assurance of product safety, such as additional warnings, contraindications, or side effects or deletions of false, misleading, or unsupportive statements; and any other changes as directed by FDA to be placed into effect immediately. These changes, proposed § 514.8(c)(3)(i)(A) and (c)(3)(i)(B), are listed in current § 514.8(d)(1) and (d)(2).

Proposed § 514.8(c)(3)(ii) permits labeling changes to the style and format that do not decrease the safety of product approved in supplemental applications to be placed into effect prior to written notice of approval from FDA of a supplemental application.

Proposed § 514.8(c)(3)(iii) updates current § 514.8(e) and describes what must be included in a supplement submitted under § 514.8(c)(3). FDA will not take action against products or sponsors solely because a change in labeling described in § 514.8(c)(3) is implemented prior to FDA receipt and approval of a supplement if the information listed in § 514.8(c)(3)(iii) has been submitted to the agency.

Proposed § 514.8(c)(4) would require applicants to notify CVM of additional designated distributors under proposed § 514.80(a)(2), (b)(3), and (b)(5)(iii) (*Records and reports concerning experience with new animal drugs for which an approved application is in effect.*—as noted in section IV.B of this document, CVM expects to publish the final rule for § 514.80 before the final rule for this document). This notification will be accompanied by a Form FDA 2301, submitted to DER, and reported at the time of initial product distribution by the new distributor. This type of change is not considered a

manufacturing change, rather a type of labeling change to be reported to the Division of Epidemiology and Surveillance in the OSC, CVM.

In addition to section 506A of the act, other sections of the act authorize FDA to propose § 514.8. Section 501 of the act (21 U.S.C. 351) prohibits the manufacture, processing, packing, or holding of drugs that do not conform to CGMP; the use of an unsafe new animal drug under the meaning of section 512 of the act; the use of unsafe color additives in or on a drug under section 721 of the act (21 U.S.C. 379e); and the distribution of a drug that differs in the strength, purity, or quality that it purports or is represented to possess. Section 502 of the act (21 U.S.C. 352) prohibits false or misleading labeling of drugs, drugs that lack adequate directions for use and adequate warnings, and the distribution of drugs that are dangerous to health when used in the manner suggested in the labeling. Under section 512 of the act, FDA will approve an application for a new intended use of a new animal drug if, among other things, the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are adequate to preserve its identity, strength, quality, and purity. Section 701 of the act (21 U.S.C. 371) authorizes FDA to issue regulations for the efficient enforcement of the act.

I. Other Information.

Proposed § 514.8(d) regarding patent information is included to comply with section 512(c)(3) of the act. Proposed § 514.8(e) regarding claimed exclusivity is included to comply with section 512(c)(2)(F) of the act. Proposed § 514.8(f) regarding good laboratory practice for nonclinical laboratory studies is redesignated as current § 514.8(l).

J. Sections Proposed for Removal

The agency is proposing that a number of paragraphs be removed after reevaluation of the regulations covering changes to an approved application because the agency has determined that these paragraphs are no longer relevant to current practices. These regulations are described in the next two paragraphs.

FDA has determined that the regulations covering special circumstances of NADA's effective prior to October 10, 1962, are no longer needed. Thus FDA is proposing to eliminate current § 514.8(g), (k), and (j).

Current § 514.8(h) stating that nothing in § 514.8 limits the Secretary of Health and Human Services's authority to suspend or withdraw approval of a new animal drug application is adequately addressed in section 512(c)(1)(F) of the act and need not be addressed in the proposed regulations. Similarly, FDA is removing current § 514.8(i) that provides for a deferral of final action on supplemental applications as described under current § 514.8(d), (e), and (g).

K. Section 514.106 Approval of Supplemental Applications

This proposal would modify § 514.106(b) regarding the administrative categorization of supplemental applications to provide for proper references to proposed § 514.8.

V. Conforming Amendments

A number of sections in the regulations covering new animal drugs are affected by these proposed changes. Conforming changes are being proposed in §§ 5.83, 25.33, 500.25, 510.300, 514.106, and 558.5 because of the reorganization of the existing information or introduction of new requirements.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs. The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The Office of Management and Budget (OMB) has determinied that this proposed rule is a significant regulatory action subject to review under the Executive Order.

The agency is proposing to amend current § 514.8 to implement section 116 of the Modernization Act. This section establishes reporting procedures and requirements for making major and other manufacturing changes to an approved NADA or ANADA. The intent of section 506A of the act and this proposed rule is to permit sponsors to use a less burdensome notification procedure for some types of changes, while also clarifying the regulations and harmonizing them, where possible, with CDER's and CBER's regulations. Downgrading the level of agency review for some of these supplements will lead to compliance cost savings due to the resulting improvement in manufacturing efficiencies.

The agency has not estimated the value of the expected improvements in manufacturing efficiencies due to the myriad of factors affecting the production schedules of new animal drugs. FDA believes, however, that these changes will result in shorter average lag times between the decision to make certain minor changes to the manufacturing process for a new animal drug and the time at which that change can be implemented. A report by the Eastern Research Group, an FDA contractor, on the effects of the human drug scale-up and postapproval change guidance for immediate release solid oral dosage form (SUPAC–IR), concluded that this type of supplement change can result in significant net savings to industry. In particular, the report found that companies gain greater control over their production resources and ''shorter waiting times for changes that can now be filed as Changes Being Effected (CBE's) or annual reports.''

The proposed rule contains four reporting categories for supplemental chemistry, manufacturing and control (CMC) changes, whereas the current regulation § 514.8 contains three. The first category concerns those changes requiring approval prior to implementation and defines what is included in a ''major'' change. These requirements are very similar to those in the existing regulation, but clarify some of the existing language. The second category is a new ''30-day changes being effected,'' or 30-day CBE category. The purpose of this new category is to provide for a less burdensome method of reporting some ''moderate'' CMC changes that previously were reported as major changes requiring approval before implementation. The firm submitting the supplement will be able to implement the change more quickly

as it will no longer require agency approval before implementation.

The third category concerns those supplement changes that can be effected upon the agency's receipt of submission of the supplemental application. The current regulation concerning this reporting category contained language that allowed for the change ''at the earliest possible time,'' while the act specifically dictates the change be allowed at the time of agency receipt of the supplement. The fourth category concerns the minor manufacturing changes and updated stability data to be submitted in an MCSR. This annual MCSR replaces the current regulation that also requires an annual report of these changes. Nevertheless, those firms currently reporting these CMC changes in the biennial supplement described previously in this document, will incur the additional burden of an extra report every other year.

Based on prior years' submissions, the agency estimates that it will receive about 906 CMC supplements. According to estimates from agency reviewers, about 755 of these would have required preapproval under the current regulation. Under the proposed rule, the number requiring preapproval is estimated at 154. The difference of 601 supplements represents the approximate number of additional changes that can be made without agency approval. Companies submitting these supplements will have the opportunity to make quicker changes and realize increased manufacturing efficiencies.

Further savings are expected from another provision of the rule that concerns labeling supplements. Currently, labeling supplements are required to include nine copies of the labeling in the submission. The proposed rule would lower this requirement to two copies, providing further small savings for industry. Although the proposal also reorganizes the rules for labeling supplements, the agency does not expect these changes to alter the number of labeling supplements submitted annually.

The creation of the MCSR may provide additional opportunity for savings because it may include minor manufacturing changes that were previously submitted as CBE's or other supplement types that require a higher level of review. Under the proposal, each firm will be able to accumulate and submit them together each year, rather than individually.

A. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact on small entities. The proposed rule implements section 506A of the act. The intent of the rule is to clarify the regulations for submitting supplemental applications for new animal drugs, harmonize the regulations with those for CDER and CBER, and lessen the compliance burden for some supplements by reducing the level of agency review necessary before implementation of certain changes. The effects of the proposed rule will be spread across all firms that submit supplements, regardless of their size. The Small Business Administration defines small businesses as businesses with fewer than 750 employees. Because these are the firms that are most likely to be submitting reports of minor changes as prior approval supplements, even though not required to do so by current regulations, rather than as biennial supplements as allowed under CVM's pilot project, they are even more likely to realize a benefit from this regulation than the larger industry members that participated in CVM's pilot project. At worst, a few small firms participating in CVM's pilot project may have to submit an annual report rather than a biennial supplement. Because the burden of submitting one additional report every other year will not impose a significant cost on small businesses, the agency certifies that the rule will not have a significant effect on a substantial number of small entities.

B. Unfunded Mandates Reform Act

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million or more (adjusted annually for inflation) in any one year. Because the agency estimates that the proposed rule will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of $100 million or more in any one year, but will result in only insignificant expenditures by the industry, and in fact should provide a net savings, it is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments 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: Supplements and Other Changes to Approved New Animal Drug Applications.

Description: As directed by the Modernization Act, FDA is proposing regulations to describe reporting procedures and requirements for making major and other manufacturing changes to an approved NADA. The proposed regulations also describe reporting procedures and requirements for making labeling changes to an approved NADA. Under proposed § 514.8(b)(2) and (c)(2), the agency will continue to require an approved supplemental application prior to distribution of a product made with a major manufacturing or labeling change to an approved NADA. Major manufacturing changes are those determined to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug. For moderate manufacturing changes, as defined in proposed § 514.8(b)(3), sponsors would be required to submit a supplemental application at least 30 days prior to distribution of the product made using the change. Under proposed § 514.8(b)(4), sponsors would not be required to submit supplemental applications for minor manufacturing changes, but would describe these changes in annual reports. Additionally, under proposed § 514.8(c)(3), certain labeling changes would require supplemental applications, but would be placed into effect immediately.

Under current regulations, CVM evaluates all manufacturing and labeling changes to approved NADA's whether they are submitted as permitted changes, CBE's, or those requiring approval prior to implementation. CVM provided greater flexibility to the

current regulations by permitting the reporting of minor manufacturing changes in a biennial supplement, as discussed earlier in this document. Changes mandated by the Modernization Act will supersede this practice, replacing the biennial supplement with an annual report, the MCSR.

The proposed rule is expected to lessen paperwork burden by requiring: (1) Fewer copies of labels for labeling changes, (2) fewer submissions because certain changes that are submitted under the current rule as individual CBE's or other supplement types may now be accumulated and submitted together once a year in the MCSR, and (3) agency approval of fewer types of changes.

Listed in Table 1 of this document is an estimate of the burden placed on industry for the various types of submissions discussed in the proposed regulation. FDA based the number of respondents upon the total number of potential sponsors. The number of total annual responses was derived from agency reviewers' estimates based upon prior years' submissions. The number of responses per respondent is an estimate that the agency arrived at by dividing the number of total responses the agency expects to receive by the total number of potential responses. Changes under § 514.8(b)(2) through (b)(4) and (c)(2) through (c)(3) are submitted on FDA Form 356V (OMB approval number 0910–0032). Labeling changes under § 514.8(c)(4) are made on FDA Form 2301 (OMB approval number 0910–0019).

Description of Respondents: Sponsors of new animal drug applications.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding this information collection by November 1, 1999, 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.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondents	Total Annual Responses	Hours per Response	Total
514.8(b)(2)(iii)	190	0.81	154	100	15,400
514.8(b)(2)(v)	190	0.59	112	80	8,960
514.8(b)(3)(i)	190	2.64	502	60	30,120
514.8(b)(3)(vi)	190	1.32	250	60	15,000
514.8(b)(4)	190	5.17	982	24	23,568
514.8(c)(2)	190	0.26	50	20	1,000
514.8(c)(3)	190	0.26	50	60	3,000
514.8(c)(4)	190	0.39	74	3	222
Total			2,174		97,270

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

IX. Comments

Interested persons may, on or before December 15, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposed rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

21 CFR Part 25

Environmental impact statements, Foreign relations, Reporting and recordkeeping requirements.

21 CFR Part 500

Animal drugs, Animal feeds, Cancer, Labeling, Packaging and containers, Polichlorinated biphenyls (PCB's).

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

21 CFR Part 558

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegate to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 5, 25, 500, 510, 514, and 558 be amended as follows:

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

1. The authority citation for 21 CFR part 5 continues to read as follows:

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282, 3701–3711a; 15 U.S.C. 1451–1461; 21 U.S.C. 41–50, 61–63, 141–149, 321–394, 467f, 679(b), 801–886, 1031–1309; 35 U.S.C. 156; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–l; 1395y, 3246b, 4332, 4831(a), 10007–10008; E.O. 11921, 41 FR 24294, 3 CFR, 1977 Comp., p. 124–131; E.O. 12591, 52 FR 13414, 3 CFR, 1988 Comp., p. 220–223.

2. Section 5.83 is amended by revising paragraph (c) to read as follows:

§ 5.83 Approval of new animal drug applications, medicated feed mill license applications and their supplements.

* * * * *

(c) The Director, Division of Manufacturing Technologies, Office of New Animal Drug Evaluation, CVM, is authorized to perform all of the functions of the Commissioner of Food and Drugs with regard to the approval of supplemental applications that are described by § 514.8(b)(2) and (b)(3) of this chapter.

* * * * *

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

3. The authority citation for 21 CFR part 25 continues to read as follows:

Authority: 21 U.S.C. 321–393; 42 U.S.C. 262, 263b–264; 42 U.S.C. 4321, 4332; 40 CFR parts 1500–1508; E.O. 11514, 35 FR 4247, 3 CFR, 1971 Comp., p. 531–533 as amended by

E.O. 11991, 42 FR 26967, 3 CFR, 1978 Comp., p. 123–124 and E.O. 12114, 44 FR 1957, 3 CFR, 1980 Comp., p. 356–360.

§ 25.33 [Amended]

4. Section 25.33 *Animal drugs* is amended in paragraph (a)(4) by removing ''514.8(a)(5), (a)(6), or (d)'' and by adding in its place ''514.8(b)(3), (b)(4), or (c)(3)''.

PART 500—GENERAL

5. The authority citation for 21 CFR part 500 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 353, 360b, 371.

§ 500.25 [Amended]

6. Section 500.25 *Anthelmintic drugs for use in animals* is amended in the first sentence of paragraph (c) by removing ''514.8(d) and (e)'' and by adding in its place ''514.8(c)(3)''.

PART 510—NEW ANIMAL DRUGS

7. The authority citation for 21 CFR part 510 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e.

§ 510.300 [Amended]

8. Section 510.300 *Records and reports concerning experience with new animal drugs for which an approved application is in effect* is amended by removing paragraph (a)(6).

PART 514—NEW ANIMAL DRUG APPLICATIONS

9. The authority citation for 21 CFR part 514 is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 356a, 360b, 371, 379e, 381.

10. Section 514.8 is revised to read as follows:

§ 514.8 Supplements and other changes to an approved application.

(a) *Definitions.* (1) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to those terms when used in this part.

(2) The following definitions of terms apply to this part:

(i) *Listed drug* means a new animal drug product that has an effective approval under section 512 of the act, which has not been withdrawn or suspended under section 512 of the act, and which has not been withdrawn from sale for what the Food and Drug Administration (FDA) has determined are reasons for safety or effectiveness. Listed drug status is evidenced by the new animal drug product's identification as a new animal drug with an effective approval in the current edition of FDA's ''FDA Approved Animal Drug Products'' (the list) or any current supplement thereto, as a new animal drug with an effective approval. A new animal drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that new animal drug product.

(ii) *Minor changes and stability report* means an annual report that is submitted to the new animal drug application or abbreviated new animal drug application once each year within 60 days of the anniversary of the application's original approval or a mutually agreed upon date. The report must include minor manufacturing and controls changes made according to § 514.8(b)(4) or state that no changes were made; and update stability data generated on commercial or production batches according to the approved stability protocol/commitment.

(iii) *Specification* means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved new animal drug application or abbreviated new animal drug application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process controls. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

(iv) *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a new animal drug as these factors relate to the safety or effectiveness of the new animal drug.

(v) *The list* means the list of new animal drug products with effective approvals published in the current edition of FDA's publication ''FDA Approved Animal Drug Products'' and any current supplement to the publication.

(b) *Manufacturing changes to an approved application*—(1) *General provisions.* (i) The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about it in a supplement under paragraph (b)(2) or (b)(3) of this section or include the information in the annual report to the application described in paragraph (b)(4) of this section.

(ii) The holder of an approved application under section 512 of the act must validate the effect of the change on the identity, strength, quality, purity, or potency of the new animal drug as these factors may relate to the safety or effectiveness of the new animal drug before distributing a drug made with a manufacturing change.

(iii) Notwithstanding the requirements of paragraphs (b)(2) and (b)(3) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or by notification in the next annual report described in paragraph (b)(4) of this section).

(iv) The applicant must include in each supplemental application providing for a change under paragraph (b)(2) or (b)(3) of this section, a statement certifying that a copy of the supplement has been provided to the appropriate FDA district office.

(v) The cover letter for a supplement or annual report described in paragraph (b)(4) of this section must include a list of all changes contained in the supplement or annual report.

(2) *Changes requiring submission and approval of a supplement prior to distribution of the product made using the change (major changes).* (i) 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.

(ii) These changes include, but are not limited to:

(A) Except as provided in paragraphs (b)(3) and (b)(4) of this section, changes in the qualitative or quantitative formulation of the new animal drug, including inactive ingredients, or other specifications as provided in the approved application;

(B) Changes requiring completion of appropriate animal studies to demonstrate the equivalence of the drug to the new animal drug as manufactured without the change or to the reference listed drug;

(C) Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(D) Changes in the synthesis or manufacture of the new animal drug substance that may affect the impurity

profile and/or the physical, chemical, or biological properties of the drug substance;

(E) Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the new animal drug product;

(F) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a new animal drug with a monoclonal antibody for the following:

(*1*) Changes in the virus or adventitious agent removal or inactivation method(s);

(*2*) Changes in the source material or cell line; and

(*3*) Establishment of a new master cell bank or seed; and

(G) Changes to a product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting the application.

(iii) The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using a change under paragraph (b)(2) of this section. Except for submissions under paragraph (b)(2)(v) of this section, the following must be contained in the supplement:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The product(s) involved;

(D) The manufacturing site(s) or area(s) affected;

(E) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation);

(F) The data derived from such studies;

(G) Appropriate documentation (for example, updated master batch records, specification sheets) including previously approved documentation (with the changes highlighted) or references to previously approved documentation;

(H) For a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols must be provided in addition to the requirements in paragraphs (b)(2)(iii)(E) and (b)(2)(iii)(F) of this section;

(I) For sterilization process and test methodologies, relevant validation protocols must be provided in addition to the requirements in paragraphs (b)(2)(iii)(E) and (b)(2)(iii)(F) of this section;

(J) A reference list of relevant standard operating procedures (SOP's) when applicable; and

(K) A claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter.

(iv) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: ''Prior Approval Supplement—Expedited Review Requested.''

(v) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of the product. The supplement, if approved, may result in the proposed change subsequently falling within a reduced reporting category because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(3) *Changes requiring submission of a supplement at least 30 days prior to distribution of the product made using the change (moderate changes).* (i) 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.

(ii) These changes include, but are not limited to:

(A) A change in the container closure system that does not affect the quality of the final new animal drug product; and

(B) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a new animal drug with a monoclonal antibody, including:

(*1*) An increase or decrease in production scale during finishing steps that involves new or different equipment; and

(*2*) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(iii) A supplement submitted under paragraph (b)(3)(i) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled ''Supplement—Changes Being Effected in 30 Days.''

(iv) Pending approval of the supplement by FDA and except as provided in paragraph (b)(3)(vi) of this section, distribution of the product made using the moderate change under paragraph (b)(3) of this section may begin not less than 30 days after receipt of the supplement by FDA. The supplement must contain the information listed in paragraphs (b)(2)(iii)(A) through (b)(2)(iii)(K) of this section.

(v) The applicant must not distribute the product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(A) The change requires approval prior to distribution of the product in accordance with paragraph (b)(2) of this section; or

(B) Any of the information required under paragraph (b)(3)(iv) of this section is missing. The applicant shall not distribute the product until FDA determines that compliance with this section is achieved.

(vi) The agency 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 product involved upon receipt by the agency of a supplement for the change. The information listed under paragraph (b)(2)(iii) of this section must be contained in the supplement. The supplement must be labeled ''Supplement—Changes Being Effected.'' These changes include, but are not limited to:

(A) Addition to a specification or changes in the methods or controls to provide increased assurance that the new animal drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess; and

(B) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product from one container closure system to another;

(vii) If the agency disapproves the supplemental application submitted under paragraph (b)(3) of this section, it

may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

(4) *Changes and updated stability data to be described and submitted in an annual report (minor changes).* (i) 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 annual report to the application in accordance with paragraph (a)(2)(ii) of this section. The report shall be labeled ''Minor Changes and Stability Report.''

(ii) These changes include but are not limited to:

(A) Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the new animal drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(B) The deletion or reduction of an ingredient intended to affect only the color of the product;

(C) Replacement of equipment with that of the same design and operating principles except for equipment used with a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a new animal drug with a monoclonal antibody;

(D) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another;

(E) A change within the container closure system for a nonsterile new animal drug product, based upon showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(F) An extension of an expiration dating period based upon full shelf-life data on full production batches obtained from a protocol approved in the application;

(G) The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application; and

(H) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint.

(iii) For changes under this category, the applicant is required to submit in the annual report a list of all products involved; and

(A) A statement by the holder of the approved application that the effects of the change have been validated;

(B) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(C) The date each change was made;

(D) Cross reference to relevant validation protocols and/or SOP's;

(E) Relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation);

(F) Appropriate documentation (for example, updated master batch records, specification sheets, etc.) including previously approved documentation (with the changes highlighted) or references to previously approved documentation; and

(G) Updated stability data generated on commercial or production batches according to an approved stability protocol.

(c) *Labeling and other changes to an approved application*—(1) *General provisions.* The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully.

(2) *Labeling changes requiring the submission and approval of a supplement prior to distribution of the product made using the change (major changes).* (i) Addition of intended uses, changes to labeling, and prescription new animal drug mailing/promotional pieces require a supplement. These changes include, but are not limited to:

(A) Revision in labeling, such as updating information pertaining to effects, dosages, side effects, contraindications, which includes information headed ''side effects,'' ''warnings,'' ''precautions,'' and ''contraindications,'' except ones described in (c)(3) of this section;

(B) Addition of intended use;

(C) If it is a prescription new animal drug, any mailing or promotional piece used after the drug is placed on the market is labeling requiring a supplemental application, unless:

(*1*) Such labeling furnishing directions, warnings, and information for use of the new animal drug are the same in language and emphasis as labeling approved or permitted; and

(*2*) Any other such labeling are consistent with and not contrary to such approved or permitted labeling.

(*3*) Prescription drug labeling not requiring an approved supplemental application is submitted in accordance with § 514.80(b)(3)(ii).[1]

(D) Any other changes in labeling, except ones described in paragraph (c)(3) of this section.

(ii) The applicant must obtain approval of the supplement from FDA prior to distribution of the product. The supplement must contain the following:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The product(s) involved;

(D) The manufacturing site(s) or area(s) affected;

(E) The data derived from studies;

(F) A claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter; and

(G) Any other information as directed by FDA.

(3) *Labeling changes to be placed into effect prior to receipt of a written notice of approval of a supplemental application.* (i) Labeling changes of the following kinds that increase the assurance of product safety proposed in supplemental applications must be placed into effect immediately:

(A) The addition to package labeling, promotional labeling, or prescription new animal drug advertising of additional warning, contraindication, side effect, and precaution information;

(B) The deletion from package labeling, promotional labeling, or drug advertising of false, misleading, or unsupported intended uses or claims for effectiveness; and

(C) Any other changes as directed by FDA.

(ii) Labeling changes (for example, design and style) that do not decrease safety of product use proposed in supplemental applications may be placed into effect prior to written notice of approval from FDA of a supplemental application.

(iii) A supplement submitted under paragraph (c)(3) of this section must include the following information:

(A) A full explanation of the basis for the changes, the date on which such changes are being effected, and plainly marked on the mailing cover and on the supplement, ''Supplement—Changes Being Effected'';

[1] § 514.80 was proposed at 56 FR 65581, December 17, 1991.

(B) Two sets of printed copies of any revised labeling to be placed in use, identified with the new animal drug application number; and

(C) A statement by the applicant that all promotional labeling and all new animal drug advertising will promptly be revised consistent with the changes made in the labeling on or within the new animal drug package no later than upon approval of the supplemental application.

(iv) If the supplemental application is not approved, FDA may order the manufacturer to cease distribution of the drug under the proposed labeling.

(4) *Changes providing for additional distributors to be reported under Records and reports concerning experience with new animal drugs for which an approved application is in effect (§ 514.80)*[2]. Supplemental applications as described under paragraph (c)(2) of this section will not be required for an additional distributor to distribute a drug that is the subject of an approved new animal drug application if the conditions described under § 514.80(a)(2), (b)(3), and (b)(5)(iii) are met.

(d) *Patent information*. The applicant shall comply with the patent information requirements under section 512(c)(3) of the act.

(e) *Claimed exclusivity*. If an applicant claims exclusivity under section 512(c)(2)(F) of the act upon approval of a supplemental application for a change in its previously approved new animal drug product, the applicant shall include such a statement.

(f) *Good laboratory practice for nonclinical laboratory studies*. A supplemental application that contains nonclinical laboratory studies shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

11. Section 514.106 is amended by removing paragraph (b)(1)(xiv) and by revising paragraphs (b)(1)(vi) and (b)(1)(xiii) to read as follows:

§ 514.106 Approval of supplemental applications.

* * * * *

(b) * * *

(1) * * *

(vi) A change in promotional material for a prescription new animal drug not exempted by § 514.8(c)(2)(i)(C)(*3*).

* * * * *

[2] See footnote 1.

(xiii) A change permitted in advance of approval as described under § 514.8(b)(3).

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PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

12. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

§ 558.5 [Amended]

13. Section 558.5 *New animal drug requirements for liquid Type B feeds* is amended in paragraph (e) by removing ''514.8(d) and (e)'' and by adding in its place ''514.8(c)(3)''.

Dated: June 23, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–25493 Filed 9–30–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 880

[Docket No. 99N-2099]

General Hospital and Personal Use Devices; Classification of the Subcutaneous, Implanted, Intravascular Infusion Port and Catheter and the Percutaneous, Implanted, Long-term Intravascular Catheter

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to classify the subcutaneous, implanted, intravascular (IV) infusion port and catheter, and the percutaneous, implanted, long-term catheter intended for repeated vascular access into class II (special controls). The agency is also publishing the recommendations of FDA's General Hospital and Personal Use Devices Panel (the panel) regarding the classification of these devices. After considering public comments on the proposed classification, FDA will publish a final regulation classifying these devices. This action is being taken to establish sufficient regulatory controls that will provide reasonable assurance of the safety and effectiveness of these devices.

DATES: Written comments by December 30, 1999. See section IX of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Patricia M. Cricenti, Center for Devices and Radiological Health (HFZ–480), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–1287.

SUPPLEMENTARY INFORMATION:

I. Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et. seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94–295), the Safe Medical Devices Act of 1990 (the SMDA) (Public Law 101–629), and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105–115) established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval). Under the 1976 amendments, class II devices were defined as those devices for which there is insufficient information to show that general controls themselves will ensure safety and effectiveness, but for which there is sufficient information to establish performance standards to provide such assurance.

The SMDA broadened the definition of class II devices to mean those devices for which there is insufficient information to show that general controls themselves will assure safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance. Special controls may include performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and any other appropriate actions the agency deems necessary (section 513(a)(1)(B) of the act).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendment devices, are classified after FDA has met the following three requirements: (1)