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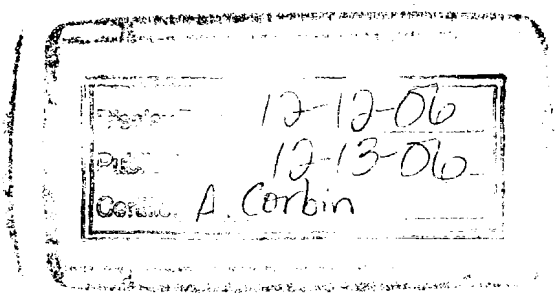

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 25, 500, 514, and 558

[Docket No. 1999N–1415] (formerly Docket No. 99N–1415)

RIN 0910–AF59

Supplements and Other Changes to Approved New Animal Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on supplements and other changes to approved new animal drug applications (NADAs) or abbreviated new animal drug applications (ANADAs) to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The final rule requires manufacturers to assess the effect of a manufacturing change on the identity, strength, quality, purity, and potency of a drug as those factors relate to the safety or effectiveness of the drug. The final rule sets forth requirements for changes requiring submission and approval of a supplement before the distribution of the drug made using the change, changes requiring the submission of a supplement at least 30 days prior to the distribution of the drug, changes requiring the submission of a supplement at the time of distribution of the drug, and changes to be described in an annual report.

DATES: The final rule is effective [*insert date 60 days after date of publication in the* **Federal Register**].

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I. Background

Section 116 of the Modernization Act (Public Law 105–115) amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a). That section describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to approved new animal drug and abbreviated new animal drug applications, and to license applications for biological products under section 351 of the Public Health Service (PHS) Act. Section 506A of the act revises current procedures for approving manufacturing changes. Major manufacturing changes, as defined in section 506A, are of a type determined by FDA to have a substantial potential to adversely affect the identity, strength, quality, purity, and potency as they may relate to the safety and effectiveness of a drug and require prior approval of a supplemental application. Under section 506A, FDA may require submission of a supplemental application for drugs made with manufacturing changes that are not major and may establish categories of manufacturing changes for which a supplemental application is required. In such a case, the applicant may begin distribution of a drug 30 days after FDA receives a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required. Under the statute, FDA may also designate a category of

manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change. Finally, FDA may also authorize applicants to distribute drugs manufactured with a change without submitting a supplemental application. The law provides that FDA may establish categories of manufacturing changes that may be made without submitting a supplemental application.

A. Development of the Regulation

In the **Federal Register** of October 1, 1999 (64 FR 53281), FDA published a proposed rule to implement section 506A of the act for NADAs and ANADAs. In that same issue of the **Federal Register** (64 FR 53393), FDA announced the availability of a draft guidance for industry entitled "Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA" (GFI #83). The guidance assists applicants in determining how they should report changes to an approved NADA or ANADA under section 506A of the act and under the proposed revisions to the new animal drug regulations pertaining to supplements and other changes to an approved application. With the issuance of this final rule, we are announcing we will issue a revised final guidance to assist applicants in determining how they should report changes to an approved NADA or ANADA under both section 506A of the act and these final regulations. The guidance has been revised to conform to the final rule and, as appropriate, to comments received. It will be issued upon approval of information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act.

B. Risk-Based Approach

The publication of this final rule is an important step in the process of adopting a risk-based approach to the regulation of drugs. In the 1990s, FDA sponsored research at the University of Maryland and other universities on the types of chemistry and manufacturing changes to immediate release solid oral drug products that could affect drug performance (i.e., identity, strength, quality, purity, and potency) and, therefore, safety and effectiveness. Using that research, FDA's Center for Drug Evaluation and Research (CDER) began to develop a risk-based approach to the implementation of manufacturing changes. Following CDER's example, FDA's Center for Veterinary Medicine (CVM) also employed a similar risk-based approach to the implementation of manufacturing changes for animal drugs. This approach provided for a continued high level of scrutiny by FDA of changes that were most likely to affect the performance of a drug and decreased scrutiny of changes that were not likely to affect the performance of a drug.

The risk-based approach was first explained in a series of guidance documents (the Scale-up and Postapproval Changes (SUPAC) guidances) that reduced the regulatory burden of obtaining FDA authorization to make certain changes. The work continued in regulations issued by the Center for Biologics Evaluation and Research (CBER) in 1997 (21 CFR 601.12). In November 1997, this risk-based approach was codified in section 116 of the Modernization Act.

This final rule implements section 116 of the Modernization Act by incorporating the statutory standards for characterizing proposed changes as having substantial, moderate, or minimal potential to adversely affect the identity, strength, quality, purity, and potency of a drug as they may relate to its safety and effectiveness and determining submission requirements based

on the potential risks associated with the changes. For changes with a substantial potential to affect the designated characteristics of a drug, FDA must review and approve a supplement that contains information showing that the proposed change will not adversely affect the drug's characteristics (i.e., information developed by the holder of the application to validate the effect of the proposed change) before distribution of the product made using the change.

It was anticipated when section 116 of the Modernization Act was written that the science of manufacturing would evolve over time and affect whether changes would be considered major or nonmajor. To accommodate future technological advancements, section 116 of the Modernization Act and this final implementing regulation both provide that FDA may, by regulation or guidance, change the designation of a particular category of change from major to nonmajor or vice versa. This concept of an evolving risk-based approach to manufacturing changes also is consistent with the agency's Good Manufacturing Practices Initiative launched in August 2002. The goals of this initiative include:

- Ensuring that state-of-the-art pharmaceutical science is utilized in the regulatory review and inspection policies;

- Encouraging the adoption of new technological advances in high quality and efficient manufacturing by the pharmaceutical industry;

- Assessing the applicable current good manufacturing practice (CGMP) requirements relative to the best quality management practices;

- Strengthening public health protection by implementing risk-based approaches that focus both industry and FDA attention on critical areas for improving product safety and quality; and

- Enhancing the consistency and coordination of FDA's drug quality oversight activities.

Specifically, one of the efforts of the CGMP initiative is to facilitate continuous improvement and innovation in manufacturing by allowing manufacturers to make certain types of changes in their processes without prior FDA approval. This rule, in keeping with that initiative, provides for a mechanism of continuous improvement through the guidance process (21 CFR 10.115) that may provide for less burdensome documentation of certain changes as manufacturing processes and pharmaceutical science develop.

II. Harmonization and Highlights of Revisions to the Proposed Rule

In the proposed rule to implement section 506A of the act for supplements and other changes to approved NADAs and ANADAs (64 FR 53281), CVM stated its intent to harmonize the reporting requirements for manufacturing changes for animal drugs with those requirements applicable to human drugs, 21 CFR 314.70. CDER published their final rule in the **Federal Register** of April 8, 2004 (69 FR 18727). CDER modified their proposed rule in response to comments received. CVM has not received similar comments to its aforementioned proposed rule. However, as a result of its harmonization effort with CDER's proposed 21 CFR 314.70, CVM has incorporated, as appropriate, many of the changes to CDER's proposed rule. This section describes the changes resulting from harmonization with CDER's final rule and other comments specific to 21 CFR 514.8. Other changes initiated by CVM are also described. Minor editorial changes are not described.

A. Section 514.8(a)—Definitions

1. Definition of "Specification" (Proposed § 514.8(a)(2)(iii))

FDA has revised the proposed definition of "specification" in § 514.8(a)(2)(iii) for consistency with CDER's regulations and has renumbered § 514.8(a)(2)(iii) through (a)(2)(v). The proposed definition included the phrase "* * *other components including container closure systems, and in-process controls." This phrase has been revised to state "components, in-process materials, container closure systems, and other materials used in the production of a drug." Thus, the revised definition is as follows: "Specification means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drugs including, for example, drug substances, Type A medicated articles, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug. For the purpose of this definition, the term 'acceptance criteria' means numerical limits, ranges, or other criteria for the tests described." See the response to comment 4 regarding the use of the terms "drug(s)," "drug substance(s)," and "drug product(s)."

2. Definition of "validate the effects of the change" (Proposed § 514.8(a)(2)(iv))

FDA has revised the proposed definition of "validate the effects of change" in § 514.8(a)(2)(iv) for consistency with CDER's regulations. The revised definition is as follows: "Assess the effects of the change means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug as these factors may relate to the safety or effectiveness of the drug." See the response to comment 3 regarding the use of the term "assess" instead of "validate."

3. Definitions of "Listed drug" and "The list" (Proposed § 514.8(a)(2)(i) and (v))

FDA has deleted the definitions of "Listed drug" (proposed § 514.8(a)(2)(i)) and "The list" (proposed § 514.8(a)(2)(v)). The definitions were originally proposed to clarify the meaning of "reference listed drug" identified under proposed § 514.8(b)(2)(ii)(B). Since the term "reference listed drug" has been deleted from proposed § 514.8(b)(2)(ii)(B), the definitions are currently not needed. See the discussion under Section B of the preamble regarding the changes to proposed section 514.8(b)(2)(ii)(B).

B. Section 514.8(b)—Manufacturing Changes to an Approved Application

Manufacturing Changes Requiring Preapproval of a Supplement (Proposed § 514.8(b)(1)(ii))

FDA has revised § 514.8(b)(1)(ii) by replacing "effect" with "effects" and deleting the phrase "* * *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* * *" because "assess the effects of the change" already is defined under § 514.8(a)(2)(i). Thus, proposed § 514.8(b)(1)(ii) is revised as follows: "The holder of an approved application under section 512 of the act must assess the effects of the change before distributing a drug made with a manufacturing change."

1. Provision of Supplemental Application to FDA District Office (Proposed § 514.8(b)(1)(iv))

FDA has revised proposed § 514.8(b)(1)(iv) to apply to both supplements and amendments as provided in CDER's regulations, § 314.70. In addition, this section also includes clarification with regard to providing a field copy for supplemental changes to drugs manufactured outside of the United States, see

the response to comment 6. The section now provides that: "In each supplement and amendment to a supplement providing for a change under paragraph (b)(2) or (b)(3) of this section, the applicant must include a statement certifying that a field copy has been provided to the appropriate FDA district office. No field copy is required for a supplement providing for a change made to a drug manufactured outside of the United States"

2. Changes That May Affect Drug Equivalence (Proposed § 514.8(b)(2)(ii)(B))

FDA has revised § 514.8(b)(2)(ii)(B) by: (1) Specifically identifying the drug as approved under section 512(b) of the act, (2) replacing "animal" in "* * *appropriate animal studies" with "clinical" to be more consistent with the language of section 506A of the act, and (3) deleting "or to the reference listed drug." Though § 514.8 applies to supplements to abbreviated new animal drug applications, FDA intends to address the term "reference listed drug" in future regulations for drugs approved under section 512(c)(2)(A) (21 U.S.C. 360b(c)(2)(A) of the act.

3. Container Closure Changes That May Affect Drug Impurity Profile (Proposed § 514.8(b)(2)(ii)(E))

FDA has limited the requirement for a prior approval supplement for drug product container closure systems to include only changes in the type or composition of a packaging component. FDA has revised § 514.8(b)(2)(ii)(E) to be similar to CDER's regulations, § 314.70, and it now states: "Changes in a drug product container closure system that controls the drug delivered to the animal or changes in the type or composition of a packaging component that may affect the impurity profile of the drug product." Unlike CDER's § 314.70(b)(vi), CVM has not included specific examples of the container

closure changes and believes that these examples are best addressed through guidance.

4. Supplement Approval Prior to Product Distribution (Proposed § 514.8(b)(2)(iii))

FDA has added the sentence, "The supplement must be labeled "Prior Approval Supplement" after the first sentence in § 514.8(b)(2)(iii) to be consistent with the submission identification requirements described in § 514.8(b)(3)(iii), (b)(3)(vi), and (b)(4).

5. Evaluate the Effects of the Change (Proposed § 514.8(b)(2)(iii)(E))

FDA has revised § 514.8(b)(2)(iii)(E) to state: "A description of the methods used and studies performed to assess the effects of the change." See the response to comment 3.

6. Validation Protocols (Proposed § 514.8(b)(2)(iii)(I))

FDA has revised proposed § 514.8(b)(2)(iii)(I) to be consistent with CDERs regulations by replacing "test methodologies" with "test methodologies related to sterilization process validation."

FDA has deleted proposed § 514.8(b)(2)(iii)(K) because submissions related to environmental considerations are addressed elsewhere in the regulations (see part 25 (21 CFR part 25)).

FDA has included § 514.8(b)(2)(iii)(J) to be consistent with section 506A(c)(1) of the act. The new section states: "Any other information as directed by FDA."

7. Protocol Submission as a Supplement (Proposed § 514.8(b)(2)(v))

FDA has revised the proposed rule to clarify that a protocol must be submitted as a prior approval supplement if the protocol was not already

included in an approved application or when changing an approved protocol. These changes are consistent with CDER's regulations, § 314.70.

8. Thirty-Day Changes-Being-Effected Supplement—Container Closure System (Proposed § 514.8(b)(3)(ii)(A))

To be consistent with CDER's regulations, FDA has revised proposed § 514.8(b)(3)(ii)(A) to clarify the wording in sections 514.8(b)(2) and 514.8(b)(4) of the proposed regulations. Revised § 514.8(b)(3)(ii)(A) states: "A change in the container closure system that does not affect the quality of the drug except as otherwise described in paragraphs (b)(2) and (b)(4) of this section."

9. Thirty-Day Changes-Being-Effected Supplement (Proposed § 514.8(b)(3)(iii))

FDA has revised proposed § 514.8(b)(3)(iii) to incorporate additional reference to § 514.8(b)(3)(vi) since "Supplements-Changes Being Effected" described under § 514.8(b)(3)(vi) must also give a full explanation of the basis of the change and identify the date on which the change is made.

10. Thirty-Day Changes-Being-Effected Supplement (Proposed § 514.8(b)(3)(v)(B))

FDA has revised proposed § 514.8(b)(3)(v)(B) to be consistent with CDER's regulations, § 314.70 and to clarify compliance with this section by allowing applicants the opportunity to amend a supplement by providing any missing information.

11. Minor Changes—Expiration Dating Period (Proposed § 514.8(b)(4)(ii)(F))

The term "full production batches" is redundant and may incorrectly imply that only the largest production batches can be used to extend an expiration dating period. Therefore, FDA has revised § 514.8(b)(4)(ii)(F) by deleting the second "full" before "production batches."

12. Minor Changes—Alternate Analytical Procedure (Proposed § 514.8(b)(4)(ii)(G))

FDA has revised § 514.8(b)(4)(ii)(G) by adding "* * *or deletion of an alternative analytical procedure" to be consistent with CDER's regulations, § 314.70.

13. Annual Report (Proposed § 514.8(b)(4)(iii))

FDA has revised § 514.8(b)(4)(iii) by deleting from the first sentence "a list of all products involved;" and adding "(A) A completed Form FDA 356V;" to be consistent with § 514.8(b)(2)(iii)(A). FDA is also adding § 514.8(b)(4)(iii)(J), "Any other information as directed by FDA" to be consistent with section 506A(d)(2)(A) of the act and making additional revisions to § 514.8(b)(4)(iii)(B) through (b)(4)(iii)(I) to be consistent with CDER's regulations, § 314.70. Most of the changes in this section are either editorial or were made to maintain consistency with other sections under § 514.8 or with CDER's regulations, § 314.70. Revisions to § 514.8(b)(4)(iii)(G) are made in response to comment 25.

C. Labeling and Other Changes to an Approved Application

1. Preapproval Supplement—Required Information (Proposed § 514.8(c)(2))

FDA has revised proposed § 514.8(c)(2)(ii)(E) by adding "* * *in support of the change" in order to clarify the scope of the derived data used to support a change. FDA has deleted proposed § 514.8(b)(2)(iii)(D) and proposed § 514.8(b)(2)(iii)(K), because submissions related to environmental considerations are addressed elsewhere in the regulations (see part 25). Additional changes are made to § 514.8(c)(2)(i) by deleting the term "prescription new animal drug mailing/promotional pieces," and to

§ 514.8(c)(2)(i)(A) and § 514.8(c)(3)(A) by replacing the term "side effect" with the term "adverse reaction."

2. 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)(iv))

FDA has revised proposed § 514.8(c)(3)(iv) to read "If the supplemental application is not approved, FDA may initiate an enforcement action because the drug is misbranded under section 502 of the act and/or adulterated under section 501 the act. In addition, under section 512(e) of the act, FDA may issue a notice of opportunity for hearing to withdraw the approval of the application." Section 514.8(c)(3)(iv) is being revised to clarify potential legal options.

III. Responses to Comments on the Proposed Rule

CVM received comments on many aspects of the proposed rule from five parties, including pharmaceutical industry associations and other interested persons. One comment to the proposed rule also fully endorsed comments by a pharmaceutical trade organization to the analogous proposed rule for human new and abbreviated new drug applications by CDER, which was published in the **Federal Register** of June 28, 1999 (64 FR 34608). These endorsed comments also are addressed in this final rule. All comments and the agency's responses are summarized below.

A. Section 514.8(a)—Definitions

1. Definition of "Minor Changes and Stability Report" (Proposed § 514.8(a)(2)(ii))

Proposed § 514.8(a)(2)(ii) states that the "Minor changes and stability report" is a 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 date of the application's original approval or mutually agreed upon date.

(1) One comment requested clarification of the requirement of submitting the minor changes and stability report noting that the time frame in the proposed provision extends before and after this agreed upon date. The commenter suggested that the requirement be revised to require submission of the report "within 60 days of the anniversary date of the application's original approval or mutually agreed upon date."

Agency Response: FDA agrees to revise the definition as requested with some modification. The definition is revised to state, in part, "* * *within 60 days before or after the anniversary of the application's original approval or mutually agreed upon date."

2. Definition of "Specification" (Proposed § 514.8(a)(2)(iii))

"Specification" is defined in proposed § 514.8(a)(2)(iii) as the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved NADA or ANADA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems and in-process controls. The proposed regulation states that the term "acceptance criteria" refers to numerical limits, ranges, or other criteria for the tests described.

(2) One comment stated that "* * *intermediates, raw materials, reagents, and other components including container closure systems and in-process materials" should be deleted from the definition of specification, with changes for these materials handled separately from the final rule and final guidance. The comment stated that the definition is not consistent with the International

Conference on Harmonization (ICH) guidance on specifications entitled "Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (ICH Q6A), which includes only drug substance and drug product. Additionally, the comment indicated that inclusion of items beyond the drug substance and drug product represents a level of complexity that would be better dealt with in guidances that can adequately evaluate the significance of changes to specific items.

Agency Response: FDA declines to revise the definition as requested. Section 512(b)(1)(D) (for NADAs) and section 512(n)(1)(G) (for ANADAs) of the act (21 U.S.C. 360b(b)(1)(D) and 360b(n)(1)(G)) require that a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of a drug be provided in an application. The regulation for the establishment of a performance standard at 21 CFR 514.1(b)(5)(v) also requires information to ensure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

Intermediates, raw materials, reagents, container closure systems, in-process materials and other materials that are used in the manufacture of drug substances, Type A medicated articles, or drug products are considered part of the manufacturing method and can have a direct effect on the identity, strength, quality, purity, or potency of the drug. While the extent of a specification (e.g., number or type of tests, strictness of acceptance criteria) for these materials may vary depending on the materials' use in a given manufacturing process, FDA has required specifications for these materials to be included in applications as part of the description of the manufacturing

method and will continue to do so. Similar to the ICH Q6A guidance, the scope of the Veterinary International Conference on Harmonization (VICH) guidance entitled "Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances" (GL39) is limited to only drug substances and drug products, whereas in this regulation the definition of "Specification" (see § 514.8(a)(2)(iii)), is intended to cover all drug materials including drug substances, drug products, raw materials, reagents, etc.

3. Definition of "Validate the Effects of the Change" (Proposed § 514.8(a)(2)(iv))

Proposed § 514.8(a)(2)(iv) defines "validate the effects of the change" to mean 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.

(3) Several comments recommended that FDA replace the terms "validate" or "validation" with "assess" or "assessment." One comment stated that although FDA is using the terms consistently with Congress' use of the terms in section 506A of the act, the term "validate" is likely to cause confusion because this term has long been associated with, and has specific meaning under, FDA's current good manufacturing practices (CGMPs) regulations.

Agency Response: FDA agrees to revise the definition as requested, as the revision makes the definition more clear without changing its meaning. FDA, on its own initiative, is also revising the phrase "* * *purity, or potency" to "* * *purity, and potency* * *" to be consistent with section 506A(b) of the act. In addition, FDA is replacing the term "assess" with "evaluate" and the "effect" with "effects." FDA notes that while the effect of a manufacturing change on the identity, strength, quality, purity and potency of a drug is to

be assessed, this assessment could involve testing of materials directly affected by a change (e.g., drug substance) in addition to or instead of drug testing. FDA has also revised § 514.8(b)(2)(iii)(E) accordingly to state: "A description of the methods used and studies performed to assess the effects of the change."

Other Changes to "Definitions" Section (Proposed § 514.8(a))

(4) Several comments requested clarification and standardization of the terms "drug product," "drug," and "product." They further suggested that "drug substance" be changed to "active pharmaceutical ingredient" (API) to be consistent with other guidances. Also, clarification of whether "product" refers to API was requested.

Agency Response: FDA agrees that terminology should be standardized throughout the proposed 21 CFR 514.8 regulations. Therefore, FDA has replaced the terms "product" and "new animal drug" with "drug" where applicable throughout 21 CFR 514.8. This change differs from the human drug regulations where the terms "product" and "drug" are replaced by the terms "drug substance" or "drug product" throughout 21 CFR 314.70. The reason for the difference is that animal drugs such as free-choice feeds (21 CFR 510.455), Type A medicated articles (21 CFR 558.3(b)(2)) and Type B or Type C medicated feed manufactured from a drug component (21 CFR 558.3(b)(5)) are not considered "drug products" as defined under 21 CFR 210.3(b)(4). However these products require approved new animal drug applications and therefore are also covered by 21 CFR 514.8. Using the term "drug product" instead of "drug" in 21 CFR 514.8 may incorrectly imply that reporting of manufacturing changes for the previously mentioned approved products is not required. The term "drug" as defined under section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) encompasses drug substances, drug products, Type A

medicated articles, etc. The terms "drug substance" and "drug products" are included in certain parts of 21 CFR 514.8, specifically in the description of changes that do not apply to free-choice medicated feeds, Type A medicated articles or Type B and Type C medicated feed manufactured from a drug component, see 21 CFR 514.8(b)(2)(ii), (b)(3)(ii), (b)(3)(vi) and (b)(4)(ii).

FDA declines to change "drug substance" to "active pharmaceutical ingredient," as requested. "Drug substance" is the commonly accepted term for filing purposes whereas the term "active pharmaceutical ingredient" is more commonly used for compliance purposes. Both terms are often used interchangeably. Since § 514.8 deals with filing issues, FDA prefers to use the term "drug substance." FDA has included a definition of "drug substance" under § 514.8(a)(2)(ii) to read "Drug substance means an active ingredient as defined under § 210.3(b)(7)."

B. Section 514.8(b)—Manufacturing Changes to an Approved Application

1. Manufacturing Changes Requiring Prior Approval of a Supplement (Proposed § 514.8(b)(1)(ii))

Proposed § 514.8(b)(1)(ii) requires the holder of an approved application to validate the effect of the manufacturing 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.

(5) One comment recommended that FDA replace the term "validate" with "assess" in proposed § 514.8(b)(1)(ii).

Agency Response: FDA agrees to revise the definition as requested.

2. Provision of Supplemental Application to FDA District Office (Proposed § 514.8(b)(1)(iv))

Proposed § 514.8(b)(1)(iv) states that an 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.

(6) One comment requested deletion of this requirement since many district offices have neither the space to store these documents nor the need for all submission documents. Any submission documents desired or required by the district office are available either from the Document Control Unit, by request from the manufacturing site, or at the manufacturing site during an inspection. Requiring copies to be sent to the district offices is a non-productive use of both industry and agency resources and effectively circumvents the goal of this rule and the intent of the Modernization Act.

Another comment requested clarification as to whether the field copy should be sent to the applicant's home district office, to the FDA office where the change is being made, or to the FDA office in the district of the company's corporate headquarters. FDA also was asked to clarify to what FDA office the copy should be sent for changes outside of the United States.

Agency Response: FDA declines to revise the regulations as suggested.

FDA disagrees that sending copies to the district offices is a non-productive use of both industry and agency resources. Instead, this requirement may reduce the burden on FDA resources (for example, searching and copying documents in the Document Control Unit by the CVM review staff), increase the awareness and interaction of district offices with FDA headquarters regarding manufacturing changes placed into effect for animal

drugs, and improve the timeliness of CGMP inspections for certain types of changes for animal drugs, if needed.

FDA also believes that this requirement is in accord with the intent of the Modernization Act, specifically section 506A of the act. That section describes requirements and procedures for making and reporting manufacturing changes. One of the requirements specified in section 506A of the act is that the holder must "validate" or assess the effects of a change before distributing a drug made with the change. In order for FDA to determine whether an applicant has made a change according to section 506A of the act, the FDA's district offices also must be informed of the effected change or change to be effected concurrently with the change being reported to FDA headquarters in a supplemental application.

Field copies should be sent to the FDA district office where the changes are being made. No field copy is required for changes made outside of the United States. Proposed § 514.8(b)(1)(iv) is amended by adding the statement "No field copy is required for a supplement providing for a change made to a drug manufactured outside of the United States"

3. Changes Listed in the Cover Letter (Proposed § 514.8(b)(1)(v))

Proposed § 514.8(b)(1)(v) adds a requirement that a list of all changes contained in a supplement or annual report described in § 514.8(b)(4) must be included in the cover letter for the supplement or annual report.

(7) Several comments requested that "cover letter" be replaced by "introduction to the document" since cover letters are not considered confidential.

Agency Response: FDA declines to revise the regulation as suggested. The standards for disclosing specific information from a cover letter or application

do not differ depending on where this information is provided or what the document is titled. Information that is exempt from disclosure (e.g., trade secret or confidential commercial information) is not disclosed whether it is in a cover letter or an application (see also 21 CFR 514.11). FDA has revised proposed § 514.8(b)(1)(v) to harmonize with the reporting requirements in CDER's regulations § 314.70(a)(6) to only require supplements to provide a list of all the changes in the cover letter. For annual reports, the list of changes may be provided in the cover letter or in the submission's summary section.

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

1. Changes That May Affect Product Sterility Assurance (Proposed § 514.8(b)(2)(ii)(C))

Proposed § 514.8(b)(2)(ii)(C) requires prior approval for 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.

(8) Several comments suggested that the language be modified to state "changes that reduce the sterility assurance level" since the impact on the sterility assurance level should be the guiding factor and the language, as proposed, is too burdensome in terms of regulatory reporting.

Agency Response: FDA declines to revise the provision as requested. The assessment as to whether a change reduces the sterility assurance is a complex and multidimensional analysis. For example, a change to a more stringent terminal sterilization process, while in theory providing a lower probability of non-sterile units, may damage the container closure system so that sterility of individual units could not be maintained. FDA also disagrees that the

proposed language is too burdensome with regard to regulatory reporting. Under the previous regulations in § 514.8(a)(2), most manufacturing and control changes, including manufacturing and control changes for sterile drug substance or drug products, required prior approval supplements. The proposed regulations allow the opportunity for applicants to report more manufacturing changes in changes-being-effected supplements or annual reports, including those manufacturing changes that will not negatively impact sterility assurance levels.

2. Changes Affecting Natural Products (Proposed § 514.8(b)(2)(ii)(F))

Proposed § 514.8(b)(2)(ii)(F) requires prior approval for 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.

(9) Several comments requested that FDA delete the reference to "natural products" since the definition of natural products is not clear and having special requirements for this additional category of products represents additional regulatory reporting requirements beyond current practice.

Agency Response: FDA declines to delete the phrase "natural products" from this provision. The changes identified in this provision are major changes and apply equally to a natural product, a recombinant DNA-derived protein/ polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody. FDA will provide a definition of natural product in the final guidance that will be published shortly, but declines to provide the definition

in the regulation because advancements in technology may require that the definition be revised.

FDA also disagrees that having special requirements for this additional category of products imposes additional regulatory reporting requirements beyond current practice. Under the previous regulations at § 514.8(a)(2), most manufacturing and control changes, including those for a natural product, DNA-derived protein/polypeptide, or a complex or conjugate of a new animal drug with a monoclonal antibody, required prior approval supplements. In the final guidance, FDA will identify changes related to these products that may now be filed in changes-being-effected supplements or annual reports. However, the three changes specified in this provision, which are unique to the identified types of drug products, are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a drug as these factors may relate to the safety or effectiveness of a drug. Virus or adventitious agent removal or inactivation processes are the means by which FDA ensures that these types of agents are removed. Failure to remove such agents has a significant potential to adversely affect public safety. Changes in source material or cell line, or establishment of a new master cell bank or seed, have a substantial potential to affect the quality of a drug substance. For example, a change in source material (e.g., species, geographic region of harvesting) could result in different impurities or contaminants (e.g., pesticides) than were previously seen or cause a change in potency.

3. Supplement Approval Prior to Product Distribution (Proposed § 514.8(b)(2)(iii))

Proposed § 514.8(b)(2)(iii) specifies the information to be included in the supplement.

(10) Several comments requested adding "as appropriate" as follows: "Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement, as appropriate." The comments said that not all listed material is relevant for every submission.

Agency Response: FDA declines to revise the provision as requested. FDA expects that the information specified in § 514.8(b)(2)(iii)(A) through (I) will be needed for many supplemental applications. FDA believes that the addition of "as appropriate" may incorrectly give the impression that this information is not routinely needed and would result in supplemental applications being submitted with insufficient information.

4. Validation Protocols for Natural Products (Proposed § 514.8(b)(2)(iii)(H))

Proposed § 514.8(b)(2)(iii)(H) states that 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 § 514.8(b)(2)(iii)(E) and (b)(2)(iii)(F).

(11) One comment requested that FDA delete the requirement for the submission of validation protocols for "natural products, et. al." because: (1) Validation protocols are maintained at the manufacturing site and are more appropriately reviewed on site, and (2) requiring submission of validation protocols only for natural products is a new and additional requirement that provides no greater assurance of safety or effectiveness of these products. The comment further stated that the additional regulatory burden is in opposition to the goals of the proposed rule and to the intent of the Modernization Act, and that there is no scientific rationale for singling out natural products under this requirement. In addition, there is no clear definition of these products,

although the accompanying guidance states that natural products include products derived from microorganisms. Many products, including antibiotics, are derived from microorganisms and have been produced and used for many years, some for decades, with adequate controls on manufacturing changes and no adverse effects. Requiring submission of validation protocols for only this single class of products is excessive.

Agency Response: FDA declines to revise the provision as requested. Unless otherwise specified by FDA, validation protocols and data need not be filed in the application but should be retained at the facility and be available for review by FDA at the agency's discretion. For most products, FDA does not require the submission of validation protocols and data. However, for a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, FDA does require the submission of validation protocols for certain critical manufacturing processes unique to these drug substances or drug products. For example, FDA would expect the validation protocol for the virus or adventitious agent removal or inactivation process to be submitted in an application. FDA currently requires this type of information to be submitted in an application. Under § 514.8(b)(1)(iii), FDA may publish future guidances to address specific filing requirements for these types of drug substances or drug products, including drug substances derived from microorganisms.

FDA also disagrees that this requirement is an additional regulatory burden and contravenes the intent of the Modernization Act. Under the previous regulations at § 514.8(a)(2), most manufacturing and control changes, including those for a natural product, required prior approval supplements. In the final guidance, FDA will identify many changes related to these products

that may be filed in changes-being-effected supplements or annual reports. As discussed previously, FDA will provide a definition of a natural product in the final guidance.

5. Validation Protocols and SOP's (Proposed § 514.8(b)(2)(iii)(I) and (J))

Proposed § 514.8(b)(2)(iii)(I) states that 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. Proposed § 514.8(b)(2)(iii)(J) states that a reference list of relevant standard operating procedures (SOPs), when applicable, must be contained in the supplement.

(12) Several comments recommended that reference to SOPs be deleted because: (1) The data represent compliance information and are better suited for field inspections, and (2) the addition of this information to existing practice would result in increased regulatory burden.

Agency Response: FDA has revised the regulation in response to the comment. An applicant is required to submit a "full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug" (sections 512(b)(1)(D) and 512(n)(1)(G) (21 U.S.C. 360b(b)(1)(D) and 360b(n)(1)(G)) of the act). This information may be submitted in different forms, including SOPs. In most cases, SOPs do not include information relevant to the NADA or ANADA review, but rather information relevant to determining an applicant's compliance with CGMPs. However, in the case of a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a new animal drug with a monoclonal antibody, or a sterilization process, information contained in SOPs is often relevant to the review of certain aspects of an application.

FDA is deleting proposed § 514.8(b)(2)(iii)(J) and is revising proposed §§ 514.8(b)(2)(iii)(H) and (I) to limit the need for information on SOPs to these situations. As discussed previously, information regarding SOPs is needed in some cases. FDA wishes to emphasize that while the information is needed for the application review, it is not always necessary to submit the actual SOP as long as the required information is provided in sufficient detail as part of the application.

6. Expedited Review of Supplement (Proposed § 514.8(b)(2)(iv))

Proposed § 514.8(b)(2)(iv) states that an applicant may request 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.

(13) Several comments requested that FDA provide feedback to the applicant on the acceptance or refusal of an "Expedited Review Request within 30 days."

Agency Response: FDA declines to revise the provision as requested. FDA intends to issue future guidance on requesting expedited reviews of supplemental manufacturing changes.

7. Protocol Submission as a Supplement (Proposed § 514.8(b)(2)(v))

Proposed § 514.8(b)(2)(v) states that 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 FDA approval prior to distribution of the product.

The supplement, if approved, may result in the proposed change subsequently falling within a reduced reporting category for the specific product because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(14) One comment recommended deleting or modifying the requirement that protocols "must be submitted as a supplement requiring approval for FDA prior to distribution of the product" because this requirement will have an effect opposite of the intent of the Modernization Act. Submission as a supplement subjects protocols to a 180-day review timeframe. Currently, such protocols are reviewed in a 30–45 day timeframe. Extending the review timeframe will delay implementation of changes contrary to the stated purpose of this rule. The comment suggested that the aforementioned requirement either should be deleted or subject to a limited 30-day review timeframe.

Agency Response: FDA declines to revise the regulation as requested. The protocols or "comparability protocols" described in proposed § 514.8(b)(2)(v) are new types of protocols for drugs and differ from the types of protocols (e.g., stability protocols) typically submitted to an investigational new animal drug file. It is expected that applicants will use comparability protocols to justify a reduced reporting category for the particular change, for example, by requesting that they be allowed to implement a major change without prior approval by FDA. These protocols, in effect, will reduce the regulatory oversight of the specified changes, and FDA considers this to have the potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug as these factors may relate to the safety or effectiveness of the drug. Also, where previously allowed by regulations, these changes were specified

as requiring prior approval, and this rule just extends that option of submitting protocols for animal drugs.

FDA has revised § 514.8(b)(2)(v) by adding the title "Comparability Protocol" to differentiate this type of protocol from other types of protocols; and has included other language to be consistent with CDER's regulations.

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

8. Thirty-Day Changes-Being-Effected Supplement (Proposed § 514.8(b)(3)(ii)(B))

Proposed § 514.8(b)(3)(ii)(B) provides for a 30-day changes-being-effected supplement for 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 a similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(15) Several comments stated that having special requirements for this category of products represents additional regulatory reporting requirements and regulatory burden beyond current practice and the intent of the Modernization Act. One comment requested that this section be removed and these changes be reported in annual reports. One comment stated that there is no scientific basis for singling out all natural products under this requirement as, for instance, microorganisms (from which some natural products are derived) form the basis of many products such as antibiotics, which have been produced and used for many years with adequate controls

on manufacturing changes and no adverse effects. Rather, this comment advocated that these types of changes be evaluated on the potential for adverse impact on safety or effectiveness of the drug product.

Agency Response: FDA declines to revise the regulation as requested. However, FDA has revised § 514.8(b)(3)(ii)(B) to specify "natural protein" rather than "natural product" to be consistent with CDER's regulations. There are specific issues and concerns relating to the production of natural protein products that are not routinely associated with other classes of drugs and, therefore, FDA has specified certain requirements for proteins. Proteins are susceptible to denaturation. Denaturation can be caused by changes in sheer force as a result of scale and/or equipment changes. Also, proteins differentially adsorb to surfaces. The identity, strength, quality, purity, or potency of the product could be affected by changes in scale or equipment because of these characteristics.

(16) Several comments requested that FDA clarify whether this section applies to drug products or drug substances.

Agency Response: FDA agrees to clarify the proposed language as appropriate. This section applies to all animal drugs, including Type A medicated articles. The terms "drug substance" and "drug product" are specifically identified if the changes do not apply to free-choice medicated feeds, Type A medicated articles or Type B and Type C medicated feed manufactured from a drug component (see response to comment 4).

(17) Several comments requested clarification of "finishing steps."

Agency Response: FDA declines to revise the regulations to provide clarification of the term "finishing steps." In general, finishing steps are considered those steps in the manufacturing process where the stability or the

property and performance of a protein product is less likely to be affected by changes in scale or equipment. The steps in a manufacturing process that would be considered finishing steps depend on the manufacturing process and the specific protein being manufactured. A particular manufacturing step may be considered a finishing step for one product but not for another. An applicant is encouraged to discuss with FDA which steps would be considered finishing steps for its particular product and process. This discussion should occur as early in the process as possible, including during INAD meetings.

(18) Several comments requested clarification of the difference between equipment that is "similar, but not identical," proposed as a changes-being-effected-in-30-days supplement, and the SUPAC terminology of equipment of the "same design and operating principle," which already is defined in the SUPAC guidance and the proposed rule as an annual report change. The comments further suggested that for equipment changes that are of different operating principle and design, FDA should consider classification within the major change category, and for equipment changes that are of the same operating principle but different design, FDA should consider classification within the moderate change category.

Agency Response: FDA agrees that replacement of equipment with that of a different design that does not affect the process operating parameters may be reported as a changes-being-effected-in-30-days supplement. Therefore, FDA is clarifying the requirement by replacing the phrase "similar, but not identical, design and operating principle" with the phrase "different design." Equipment of a different design may or may not have a different operating principle.

FDA is also revising section 514.8(b)(3)(ii)(B)(*2*) by deleting "new or" since new equipment may not necessarily be different equipment in regard to process methodology or process operating parameters.

9. Supplement—Changes Being Effected (Proposed § 514.8(b)(3)(vi))

Proposed § 514.8(b)(3)(vi) states that 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 begin distribution of the drug 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: (1) 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 (2) 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.

(19) Several comments recommended that FDA add "a sterile drug product or a sterile drug substance" to expand the type of drug products for which the container changes allowed in this section would apply, since size and shape changes for sterile API and drug products have only moderate potential impact. This is especially true when the size/shape changes are very minor in nature, as is often the case when suppliers make minute adjustments in their packaging components.

Agency Response: FDA declines to revise the regulation as requested. Sterility of drug products is a fundamental and essential quality attribute of

these drugs and is a critical aspect of the safety assessment. Changes in the container closure system, even if minimal, may affect the sterility assurance of the drug product and are considered major changes. FDA acknowledges that the effects of changes in the size and/or shape of the container closure system for sterile drug substances are considered by FDA to be a lower risk than for sterile drug products because of the differences in procedures for sterilizing drug substances and finished drug products. However, they are still of a higher risk than for nonsterile products. Therefore, FDA declines to specify in the regulations that these changes can be submitted in a changes-being-effected supplement. Additional information on changing container closure systems for drug products is included in the final guidance.

10. Disapproved Supplements and Drug Distribution Stoppage (Proposed § 514.8(b)(3)(vii))

Proposed § 514.8(b)(3)(vii) provides that if the agency disapproves the supplemental application submitted under paragraph (b)(3) of this section, the agency may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

(20) Several comments recommend replacing the language in § 514.8(b)(3)(vii) with "If FDA later determines that the supplemental application is not immediately approvable, the agency will work with the applicant to resolve all issues and to assure the continued availability of the drug," since this is the current practice and the intent of the U.S. Senate as recorded in Senate Report 105–43.

Agency Response: FDA declines to revise the provision as requested. The regulation is consistent with section 506A(d)(3)(B)(iii) of the act, which allows

FDA to disapprove a supplemental application and order the manufacturer to cease distribution of the drug made with the change.

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

1. Minor Changes Documented in an Annual Report (Proposed § 514.8(b)(4)(ii)(A))

Under proposed § 514.8(b)(4)(ii)(A), the following type of change must be documented in the next annual report: 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.

(21) Several comments requested that FDA change this requirement to read "Any change to comply with an official compendium." One of these comments added that: (1) Section 501(b) of the act requires the FDA to resolve any differences with the compendial body, the United States Pharmacopoeia (USP), (2) it is unfair to place the applicant in the middle of these discussions, and the compendial review process should be the mechanism by which the FDA has influence, and (3) it should be permitted and appropriate that any USP-adopted changes, including changes that may relax acceptance criteria and/or analytical procedures, be updated via an annual report, with both the innovator as well as any generic companies subject to this requirement. Another one of these comments added that FDA's proposed regulations are inconsistent with the statutory structure for drug approval and quality, and that requiring supplements for labeling changes consistent with compendial

revisions would likely cause confusion and uncertainty about a product's legal status and further impose unnecessary, burdensome requirements on industry.

Agency Response: FDA declines to revise the provision as requested, but is revising the regulations to provide further clarification. The basis for this decision is set forth as follows.

Under section 501(b) of the act (21 U.S.C. 351(b)), a drug that is recognized in an official compendium may be considered adulterated if its strength differs from, or its quality or purity falls below, the standards set in the compendium. Determinations of adulteration under this provision of the act must be made in accordance with the analytical procedures prescribed in the compendium, except when there is no analytical procedure prescribed in the compendium or if the tests prescribed in the compendium are insufficient and the agency has gone through the process outlined in the statute and has issued a regulation to provide an appropriate analytical procedure. No drug defined in an official compendium will be considered adulterated under section 501(b) of the act because its strength differs from, or its quality or purity falls below, the standards set in the compendium if the differences from the standard are stated in its label. Under section 502(g) of the act (21 U.S.C. 352(g)), a drug that is recognized in an official compendium may be considered misbranded if the drug is not packaged and labeled as prescribed in the compendium.

FDA is aware of the legal status of the United States Pharmacopoeia/ National Formulary (USP/NF) under the act as a standard for determining whether a drug may be considered adulterated or misbranded. A compendial product that fails to comply with USP/NF standards may be considered to be adulterated or misbranded under the act. However, a compendial product can

still be considered adulterated or misbranded under other provisions of sections 501 or 502 of the act, even if it complies with USP/NF standards.

Thus, while the standards in the USP/NF are legally enforceable standards for determining whether a drug is considered adulterated under section 501 of the act, these standards are not considered the complete regulatory specifications. FDA is responsible for establishing regulatory specifications as part of the approval of an application. Under section 512(b)(1)(D) and 512(n)(1)(G) (21 U.S.C. 360b(b)(1)(D) and 360b(n)(1)(G)) of the act, an application must include a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the drug. If the specifications included in the application are considered inadequate to ensure and preserve the identity, strength, quality, purity or potency of the drug, FDA will refuse to approve the application. Standards established by an official compendium may be inadequate for the purposes of approving an application under sections 512(d)(1) and 512(c)(2)(A) (21 U.S.C. 360b(d)(1) and 360b(c)(2)(A)) of the act. The USP acknowledges that "[w]hile one of the primary objectives of the Pharmacopoeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the sources of the material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided

in the individual monograph." (U.S.P. 29, General Notices, Foreign Substances and Impurities).

Not all compendial standards or changes in existing compendial standards are adequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, or are consistent with other requirements of the act. For example, a deletion of an impurity test may result in an inadequate standard for ensuring the purity of the drug. Therefore, FDA does not believe that all changes made to comply with an official compendium are of a type that should be reported in an annual report.

Analytical procedures: For compendial drugs, the determination of whether the drug is adulterated under section 501(b) of the act must be made in accordance with the analytical procedures set forth in the compendium, except when there is no analytical procedure prescribed in the compendium or if the tests prescribed in the official compendium are insufficient. In these situations, FDA can follow the process outlined in the statute and issue a regulation to provide an appropriate analytical procedure. Because of the legal status of compendial analytical procedures in the act and other requirements relating to analytical procedures in the statute, FDA concurs that changes in analytical procedures to comply with an official compendium may be filed in an annual report except for changes to comply with an official compendium that result in the deletion of a test or the relaxation of an acceptance criterion and has revised the regulation accordingly. FDA wishes to emphasize that under FDA's CGMP regulations, the suitability of all analytical procedures, including compendial procedures, must be verified under actual conditions of use. For example, an assay analytical procedure where degradation products, impurities, or excipients interfere with the analysis is not considered an

acceptable analytical procedure. The use of unacceptable analytical procedures, even if specified in an official compendium, can be considered a violation of the act. FDA also wishes to emphasize that a change from an approved analytical procedure that is capable of quantifying impurities to a compendial analytical procedure that cannot quantify impurities is in essence a deletion of an impurities test. This change of procedure should not be reported in an annual report, but should be reported as any other request for deletion of an approved test.

Tests and acceptance criteria: Under sections 512(b)(1)(D) and 512(n)(1)(G) of the act, an application must include a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the drug. If the specifications included in the application are considered inadequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, the agency will refuse to approve the application. As previously discussed, the standards established by an official compendium may be inadequate for the purposes of approving an application under sections 512(d)(1) and 512(c)(2)(A) (21 U.S.C. 360b(d)(1)(C) and 360b(c)(2)(A)(i)) of the act.

As part of the detailed application review process and in accordance with section 512 of the act, FDA requires tests and acceptance criteria that the agency believes are necessary to ensure and preserve the identity, strength, quality, purity, and potency of the product. The specifications included in the approved application are legally binding upon the applicant, and a product that fails to comply with the specifications included in the approved application can be considered an unsafe new animal drug under section 512(a)(1) of the act. Compendial standards are often used in evaluating the

specifications proposed in the application. However, compendial standards often must be supplemented with additional tests, such as a specific test for impurities, to ensure the identity, strength, quality, purity, and potency of the drug. Also, the tests and acceptance criteria in an application are often approved without the benefit of a compendial standard for a drug because no compendial standard has been established. Situations could arise where, for example, FDA requires tests and acceptance criteria for specific impurities as part of approval of an application. These impurities are not specified in an existing monograph or are not included in a monograph published subsequent to the approval of the drug. If FDA allowed all changes that comply with an official compendium to be included in an annual report, the applicant could interpret this provision as allowing it to delete the tests that are required as a condition of approving the application.

A change to relax an acceptance criterion or delete a test is considered a major change. FDA needs to review a request for this type of change in the context of a particular NADA or ANADA to determine if the change will adversely affect the identity, strength, quality, purity, or potency of the drug. Changes such as these, when requested solely at the discretion of the applicant, must be filed in a prior approval supplement. Reporting these changes in an annual report is not appropriate. However, when a change to relax an acceptance criterion or delete a test is made to comply with a change to an official compendium, the change is considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. The change is considered to be moderate because: (1) The change has been reviewed by an independent, impartial group that has the goal of promoting

public health, and (2) FDA has had the opportunity through the USP process of reviewing the proposed change in general, but not necessarily in the context of each individual application affected by the change. Therefore, FDA will require a changes-being-effected-in-30-days supplement for a change to relax an acceptance criterion or delete a test to comply with a change to an official compendium. A change made to comply with an official compendium that results in a tightening of an approved acceptance criterion or an addition of a test may be filed in an annual report.

The provisions in the final rule for changes to comply with an official compendium might be viewed by some as an increase in burden over how FDA has been interpreting its regulations regarding supplements in the past. However, FDA believes that the provisions are necessary and consistent with the requirements of section 506A for the establishment of the reporting category for a change based on the change's potential to adversely affect the identity, strength, quality, purity, or potency of a drug as these factors may relate to the safety or effectiveness of the drug.

For the reasons discussed previously, the agency is adding § 514.8(b)(3)(ii)(C) as follows: "Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements." The agency also is revising § 514.8(b)(4)(ii)(A) as follows: "Any change made to comply with an official compendium, except a change in paragraph (b)(3)(ii)(C) of this section, that is consistent with FDA statutory and regulatory requirements."

2. Minor Changes—Replacement of Equipment (Proposed § 514.8(b)(4)(ii)(C))

Under proposed § 514.8(b)(4)(ii)(C), the following minor change must be documented in the next annual report: 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.

(22) One comment requested deleting the words "except for equipment used with a natural product, a recombinant DNA-derived protein/polypeptide product." According to the comment, singling out these products by requiring a higher classification for these changes is inappropriate, as there is no scientific basis for a blanket application of this distinction and all changes should be assessed on their potential for adverse affects on the safety or effectiveness of the product. The comment further stated that equipment for natural products (as defined in this rule) should be evaluated on the same basis as that for all other products.

Agency Response: FDA declines to revise the regulation as requested, but has revised it to provide clarity by referencing section (b)(3) in regard to exceptions for equipment replacement. As discussed in the response to comment 15, there are specific issues and concerns for these drugs as a result of scale and/or equipment changes not routinely associated with other classes of drugs. Changes to identical equipment used in the production of proteins could be reported in an annual report. However, a change to equipment of the same design and operating principle, but not identical equipment (e.g., capacity), is not considered a minor change for protein products.

3. Minor Changes—Container Changes (Proposed § 514.8(b)(4)(ii)(D))

Under proposed § 514.8(b)(4)(ii)(D), the following minor change is documented in the next annual report: 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.

(23) Several comments recommended deleting "containing the same number of dosage units." According to the comments, for nonsterile dosage forms, the fill count of the bottle should be allowed to be changed along with the size/shape. The current language would allow size of the bottle to increase (resulting in more headspace) but the fill count to not equivalently change.

Agency Response: FDA declines to revise the regulation as requested. Due to the differences and complexities of labeling issues for animal drug products versus human drug products, regulation of labeling changes is not being harmonized with human drug product regulations. However, information regarding the reporting of labeling and other types of changes to animal drug products has been updated and consolidated under § 514.8(c). Labeling changes related to manufacturing changes, e.g., changes to the labeled storage conditions, will be identified in the final guidance.

4. Minor Changes—Code Imprints (Proposed § 514.8(b)(4)(ii)(H))

Under proposed § 514.8(b)(4)(ii)(H), the following minor change is documented in the next annual report: 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.

(24) A few comments requested that FDA revise this provision to allow the addition of an ink imprint. Another comment said it is not clear whether the provision includes ink printing, and a cross-reference to part 206, Imprinting of Solid Oral Dosage Form Drug Products for Human Use, may also be helpful. One comment requested that wording should be added to allow for ink printing on modified dosage forms, as this should not impact drug release.

Agency Response: FDA declines to revise the regulation as requested and is clarifying that inks are not included in this provision. FDA believes that any recommendations on how to report the addition of inks is best handled in guidance documents so that the issues and conditions associated with such changes can be fully explained. For example, FDA would expect that any colors used in ink imprint would be listed for use in or on a drug in FDA regulations (see 21 CFR parts 73, 74, 81, and 82).

5. Annual Report—Required Information (Proposed § 514.8(b)(4)(iii))

Proposed § 514.8(b)(4)(iii) requires the applicant to submit in the annual report a list of all products affected by a change in this category, and: (1) A statement by the holder of the approved application that the effects of the change have been validated; (2) a full description of the manufacturing and control changes, including the manufacturing site(s) or area(s) involved; (3) the date each change was made; (4) cross reference to relevant validation protocols and/or SOP's; (5) 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); (6) appropriate documentation (for example, updated master batch records, specification sheets, etc.) including previously approved documentation (with the change highlighted) or references to previously approved documentation; and (7) updated stability data generated on commercial or production batches according to an approved stability protocol.

(25) Several comments recommended that the reference to SOPs and the term "validation" be deleted, and that the agency also eliminate the requirements that the applicant submit the date each change was made and cross reference to relevant validation protocols and/or SOPs, as the data

represent compliance information and are better suited for field inspections. The comments asserted that the addition of this proposed information to existing practice would result in increased regulatory burden.

Agency Response: FDA is revising the provision to clarify when validation protocols and SOPs are needed. The agency's response to comment 26 addresses the recommended deletion of providing the date each change was made. As discussed with regard to comment 11, validation protocols and data need not be filed in the application, unless otherwise specified by FDA, but should be retained at the facility and be available for review by FDA at the agency's discretion. For most drugs, FDA does not require the submission of validation protocols and data. However, for a natural protein, a recombinant DNA-derived protein/polypeptide, a complex or conjugate of a drug substance with a monoclonal antibody, or sterilization process, FDA does require the submission of validation protocols for certain critical manufacturing processes unique to these drugs. In addition, an applicant is required to submit a full description of controls used for the manufacture, processing, and packing of a drug (sections 512(b)(1)(d) and 512(n)(1)(G) of the act). This information may be submitted in different forms, including SOPs. In most cases, SOPs do not include information relevant to the NADA or ANADA review, but rather information relevant to determining an applicant's compliance with CGMPs. However, in the case of a natural product, a recombinant DNA-derived protein/ polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, or a sterilization process, information contained in SOPs is often relevant to the review of certain aspects of an application.

6. Annual Report—Provision of Date(s) of Changes (Proposed § 514.8(b)(4)(iii)(C))

(26) One comment recommended that § 514.8(b)(4)(iii)(C), which provides that the date each minor change is made be submitted in an annual report, be modified to state "Either the date each change was made or the first lot produced using the change." The comment suggests that for processes that take several days, the first lot number is more appropriate than the date. The lot number allows traceability through the entire process to better determine the effect of the change.

Agency Response: FDA declines to revise the regulation as requested. The date when a change is made is important to identify the production batches that may be affected by the change. This is important for various reasons; for instance, it allows reviewers to easily compare data generated at different times to determine if there are any changes or trends in product quality over time. The reporting of a lot number may not readily indicate to the reviewer the date the change was made.

7. Annual Report—Appropriate Documentation (Proposed § 514.8(b)(4)(iii)(F))

(27) One comment stated that requiring the submission of batch records with changes highlighted is an unnecessary additional burden that will not increase the assurance of the safety, purity, or effectiveness of products, and is in contravention of the goals of the proposed rule and the intent of the Modernization Act. Batch records may be issued or reissued to correct minor typographical errors or to clarify instructions. Several versions may be issued in 1 year. Requiring the highlighting of all of these changes in the annual update is unnecessary, as batch records and their history are maintained at the manufacturing site and are available for review during inspections.

Agency Response: FDA declines to revise the regulation as requested. Under § 514.8(b)(1)(v), FDA is requiring that a list of changes be provided in both supplemental applications and annual reports. FDA proposed this requirement as a means to more efficiently locate and identify changes in what are often substantial documents. It is expected that any change to an approved document (e.g., master batch record, raw material specification sheet, analytical method procedure, etc.), other than a minor editorial or format change, results in an updated document that must be included as part of the supplemental application or annual report. Highlighting the proposed or implemented change(s), other than editorial or format change(s), will allow the reviewer to easily review and assess the impact of these change(s), if any, on the identity, strength, quality, purity or potency of a drug as these factors may relate to the safety or effectiveness of the drug. For changes reported in the annual report, it is expected only the most recently revised document at the time of preparation be submitted with the minor changes highlighted and with a copy of the previously approved document (or reference to where this document can be found in the new animal drug file).

Section 506A(d)(2)(A) also states in part that a holder making a certain type of manufacturing change shall submit a report on the change "which shall contain such information as the Secretary determines to be appropriate* * *." Therefore, for new animal drugs, FDA determines that this requirement is appropriate for ease of review and assessment of the impact of a minor change(s).

F. Labeling and Other Changes to an Approved Application

1. Approved Application—Labeling and Other Changes (Proposed § 514.8(c))

Proposed § 514.8(c) describes labeling and other changes to an approved application.

(28) One comment stated that this section appears to eliminate the ability to report minor changes to labeling in an annual update. According to the comment, label changes are classified as major changes (§ 514.8(c)(2)) or requiring a written notice of a supplemental application—Changes Being Effected (§ 514.8(c)(3)). It is requested that this section be clarified and the opportunity to submit minor changes in an annual update be added. Labeling changes unrelated to product effectiveness or safety should be permitted as minor changes and included in annual reporting. The accompanying guidance document should be expanded to address labeling changes.

Agency Response: FDA declines to revise the provision as requested. However, FDA agrees that a few labeling changes (e.g., changes to the labeled storage condition to be submitted in a prior approval supplement) are more appropriately reported to and reviewed by FDA/CVM's Division of Manufacturing Technologies in either a prior approval supplement, changes-being-effected supplement, or annual report, i.e., minor changes and stability reports. Labeling changes more appropriately submitted to the Division of Manufacturing Technologies, including those labeling changes that can be reported in an annual report, will be described in the final version of the companion guidance document. Labeling changes (for example, design and style) that do not decrease safety of drug use and that are proposed in supplemental applications may be placed into effect prior to written notice of approval from FDA of a supplemental application (§ 514.8(c)(3)(ii)).

2. Approved Applications—General Provisions for Labeling and Other Changes (Proposed § 514.8(c)(1))

Proposed § 514.8(c)(1) states that 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.

(29) One comment recommended that the statement "Any change made in labeling to comply with an official compendium may be submitted in the annual report" be included in proposed § 514.8(c)(1) as follows: "(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. Any change made in labeling to comply with an official compendium may be submitted in the annual report."

Agency Response: FDA declines to revise the provision as requested. While the labeling requirements in the USP/NF are legally enforceable standards for determining whether a product is misbranded under section 502 of the act, use of these standards alone does not ensure compliance with the act. Moreover, the USP states that "Articles in this Pharmacopoeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopoeial requirements set forth for the articles." (U.S.P. 29, General Notices, Labeling).

3. Labeling Changes and § 514.80 (Proposed § 514.8(c)(2)(C)(3))

Proposed § 514.8(c)(2)(C)(3) provides that the prescription drug labeling not requiring an approved supplemental application is submitted in accordance with § 514.80(b)(3)(ii). Proposed § 514.8(c)(4) describes "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). According to § 514.8(c)(4), supplemental applications as described under § 514.8(c)(2) 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.

(30) One comment recommended that the reference to § 514.80 be removed since it refers to a non-existent rule.

Agency Response: The final rule for § 514.80 was published on March 31, 2003 (68 FR 15365). Therefore, the agency is retaining the reference to § 514.80.

G. Implementation of the Final Rule and Guidance

(31) One comment recommended that the proposed rule and draft guidance be withdrawn in order to allow development of a revised proposed rule and associated industry guidance that clearly reflect the intent of Congress, as required by the Modernization Act. The comment also encouraged FDA to work in collaboration with the industry in crafting improved versions of these important regulations. The comment contends that the proposal and guidance fails to address and fulfill the intent of the Modernization Act, a substantial number of individual issues in the proposed rule and guidance require revision, there was a lack of industry and public involvement in drafting the documents, and the time provided by FDA for the evaluation, comment, and considered revisions was too short.

Agency Response: FDA declines to withdraw the proposed rule and guidance. FDA's procedures for rulemaking are governed by the Administrative Procedure Act (5 U.S.C. 553) and set forth in FDA regulations at 21 CFR 10.40

and 10.80. Guidances are developed in accordance with FDA's good guidance practices (GGPs) (see the **Federal Register** of September 19, 2000 (65 FR 56468) and 21 CFR 10.115). As discussed previously in this document, the use of guidance documents will allow FDA to more easily and quickly modify and update important information. Moreover, section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug. In the October 1, 1999 proposal, FDA proposed to implement section 506A of the act for NADAs and ANADAs. In that same issue of the **Federal Register**, FDA announced the availability of a draft guidance for industry entitled "Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA" to assist applicants in determining how they should report changes to an approved application. FDA allowed for public participation in the development of the regulation and guidance consistent with FDA regulations and policy and to the extent practicable. The time period to provide public comment was consistent with FDA's regulations and statutory requirements. FDA also held a public meeting on August 19, 1999, to hear comments on the guidance and the proposed rule. FDA has carefully considered the public comments and believes that the final regulation and guidance provide for significant reduction in regulatory burden and comply fully with section 506A of the act.

(32) One comment noted that the animal drug industry has been very pleased with the successful 1996 CVM initiative, "Alternate Administrative Process for the Implementation and Submission of Supplemental Chemistry, Manufacturing and Control Changes (AAP)," and their support of the Modernization Act was given based on their legal interpretation that the

Modernization Act did not preclude the continuation of the AAP program. The comment further stated that the AAP program very succinctly provided a process for determining minor supplemental chemistry, manufacturing, and control changes that are reported on a biennial basis; as such, the concepts embodied in the AAP are strongly supported. There is concern that implementation of the proposed rule will be more burdensome than the AAP on both FDA and industry. Therefore, the proposed rule will be a significant step backwards.

Agency Response: The AAP program has been superseded by section 506A of the act and the revised § 514.8 regulations. Section 506A of the act does not allow for the reporting of minor manufacturing changes in biennial supplements (as allowed in the AAP program) rather than annual reports. FDA disagrees that the proposed rule will be a significant step backwards from the AAP program since the proposed rule and supporting guidance will allow more flexibility in the reporting of moderate changes in immediate changes-being-effected or 30-day-changes-being-effected supplemental applications. Implementation of moderate changes under the past regulations or under the AAP program would have required a prior approval supplement and would not have been considered appropriate for filing under the AAP program.

H. General Comments

(33) Several comments argued that the proposal does not meet the intent of Congress or Section 116 of the Modernization Act. The comments stated that Congress expected substantial improvement in the management of technical supplements for manufacturing changes, but that: (1) The proposed rule does not provide significant regulatory relief, (2) significant numbers of additional new categories of manufacturing changes requiring prior approval

supplements have been added without evidence of the need or a scientific rationale for such additional requirements, (3) there are no new approaches to the regulations and guidances for manufacturing changes, and (4) the reporting burden would be substantially increased.

Agency Response: FDA believes that these regulations are consistent with the intent of Congress and the regulatory requirements and reporting categories are consistent with section 506A of the act. The regulations provide a new approach to regulating post-approval manufacturing changes. The approach is based on the potential for a change to adversely affect the identity, strength, quality, purity, or potency of the drug as these factors relate to the safety or effectiveness of the drug. The regulations and its companion guidance will provide significant regulatory relief by allowing post-approval manufacturing changes to be implemented more rapidly, while still ensuring the identity, strength, quality, purity, and potency of the drug. Under this final rule, many of these same changes can now be reported in changes-being-effected supplements or annual reports. In contrast, under the previous regulations, almost all manufacturing changes required FDA approval prior to implementation. As an example, the previous regulations required prior approval for all manufacturing site changes for drug products. Now, fewer types of animal drug manufacturing site changes will require submission in prior approval supplements. Many will be submitted in a changes-being-effected-in-30-days supplement or in the annual report.

(34) Several comments stated that if appropriate studies comparing pre- and post-change material are performed (as required) and no evidence of an adverse effect is found, then a reduced reporting structure for the evaluated change is appropriate. One comment added that the FDA should adopt a

"decision tree" or "key questions" approach in implementing Section 116 of the Modernization Act. The decision tree approach would base regulatory reporting requirements on the results of scientific comparison of the quality of a drug product both pre- and post-change. Thus, the decision tree would focus on answering key questions rather than producing an exhaustive categorization of potential types of changes.

Agency Response: FDA agrees that decision trees are a viable approach to post-approval manufacturing changes. However, a decision or decision tree that does not consider the potential for a change to have an adverse effect is not consistent with section 506A of the act. The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of the assessment studies. In some cases, based on the potential for an adverse effect, FDA would expect to review a change prior to distribution of the drug made with the change, even if the applicant concludes that its studies and data demonstrate that the change has no significant adverse effect. FDA must evaluate whether the studies performed by the applicant are sufficient to assess the effects of the change, and that the data support the applicant's claim that the change has not adversely affected the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety and effectiveness of the drug.

FDA regulates a wide range of products, and a decision tree should address the fact that the potential for an adverse effect will vary depending on such factors as the dosage form and route of administration. For example, in general, a packaging change that involves a parenteral drug product is viewed by FDA to have a higher potential to cause an adverse effect on the quality of the drug product as it relates to the drug's safety and effectiveness than a packaging

change for a solid oral dosage form product. One rationale for FDA's increased concern is that leaching from packaging for parenteral drug products is more likely to occur than for solid oral dosage forms; therefore, a higher potential for adverse reactions due to the route of administration may occur. A safety determination by FDA must be made. A decision tree that does not address these differences in the potential for a change to adversely affect the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug would not be consistent with section 506A of the act.

(35) Several comments stated that FDA has not presented evidence of the substantial adverse impact of the proposed rule and the accompanying draft guidance. The requirement for FDA to present such evidence was a clearly stated expectation during the development and enactment of the manufacturing provisions of the Modernization Act.

Agency Response: FDA has examined the impact 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). The discussion of the analysis of impacts is in section VII of the preamble to the final rule.

(36) Several comments resubmitted comments previously provided to the agency on the draft guidances entitled "BACPAC I," "Changes to an Approved NDA or ANDA," and "Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA," requesting that FDA consider these comments in finalizing the proposed regulation.

Agency Response: FDA has considered the resubmitted comments to the extent that they were applicable to the proposed regulation.

(37) Another comment stated that FDA should provide for realistic and workable filing mechanisms and requirements with regard to changes in the manufacture of drug substances where the relevant information already is included in drug master files.

Agency Response: The regulations and companion guidance for industry provide recommendations on reporting changes in the conditions established in an approved application, including changes in the drug substance covered by master files. Issues relating to master files and how these are used in the application review process are outside the scope of this regulation.

IV. Unrelated Referenced Comments to the Proposed Rule

(Comments (38) through (40)). One comment recommended for the human drug regulations under § 314.70(b)(2)(v) that "labeling" be clarified to "drug product labeling" Another comment suggested that the final sentence in § 314.70(c)(1) be changed to "If the change concerns labeling only, include." Yet another comment recommended that the phrase "* * *a distributor's name or editorial changes to comply with an official compendium" be added to § 314.70(d)(2)(x).

Agency Response: These comments are outside the scope of this final rule. Therefore, the agency declines to address them at this time.

V. Conforming Amendments

FDA has made conforming changes in §§ 25.33, 500.25, 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 25.30(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 final rule under Executive Order 12866 and 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). The agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small businesses will likely incur a net benefit while only incurring negligible costs, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

FDA proposed amendments to 21 CFR 514.8 that would implement section 506A of the act (64 FR 53281). 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 is to permit sponsors to use a less burdensome notification procedure for some types of manufacturing changes. Downgrading the level of agency review for some of these supplements is expected to lead to compliance cost savings due to the resulting improvement in manufacturing efficiencies. This final rule makes some minor changes to the proposed rule but does not alter the basic reporting structure as outlined in the proposal.

Although the proposed rule would have increased manufacturing efficiencies, we did not estimate the value of the expected improvements due to the myriad of factors affecting the production schedules of animal drugs. Comments to the proposed rule have not provided any more data or arguments that add to, or refute, this position. Therefore, we retain it for this final rule. The final rule will result in shorter average lag times between the decision to make certain changes to the manufacturing process for an animal drug and the time at which that change can be implemented. A report by the Eastern Research Group (ERG), an FDA contractor, on the effects of the human drug Scale-Up and Post-Approval Change Guidance for Immediate Release Solid Oral Dosage Form (SUPAC-IR), concluded that this type of supplement change often results 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 (CBEs) or annual reports" (Ref. 1).

We received many comments to the proposed rule that stated that the new supplement reporting structure would impose new reporting burdens on industry. Those comments have been addressed previously in this preamble. Our interpretation of the current regulations leads us to conclude that this final rule would not impose more than minimal additional reporting burdens, as described in the proposed rule and this section. Further, the final rule retains and reiterates our initial estimate of the number of manufacturing changes that could be made more quickly as a result of the lower level of agency review of certain manufacturing supplements.

The final 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 constitutes 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 supplemental changes that can be effected upon receipt by FDA 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 Modernization Act specifically dictates that 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 a periodic minor changes and stability report (MCSR). This annual MCSR replaces the current regulation that also requires an annual report of these changes.

Based on prior year submissions, the agency estimates that CVM will receive about 1,188 CMC supplements annually. According to estimates from agency reviewers, about 755 of these would have required preapproval under the current regulation. Under the final rule, the number requiring preapproval is estimated at 234. The difference of 521 supplements represents the approximate number of additional changes that can be made without prior 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 final rule would lower this requirement to two copies, providing further savings for industry. Although this rule 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 annual MCSR may provide additional opportunity for savings because it may include minor manufacturing changes that were previously submitted as CBEs or other supplement types that require a higher level of review. Under the final rule, each firm will be able to accumulate and submit them together each year, rather than individually.

Regulatory Flexibility Analysis

The Regulatory Flexibility Act (as amended by the Small Business Regulatory Enforcement Fairness Act) requires agencies to analyze regulatory options to minimize any significant impact on small entities. The final rule implements section 506A of the act. The intent of the rule is to clarify the regulations for submitting supplements to new animal drugs applications, harmonize the regulations with those for human drugs, and lessen the compliance burden for some supplements by reducing the level of agency review necessary before implementation of the change. The effects of these changes will be spread across all firms that submit supplements, regardless of their size. The Small Business Administration limits small businesses affected by this final rule to those manufacturers with fewer than 750 employees. In the proposed rule, the agency certified that the rule will not have a significant effect on a substantial number of small entities. This certification was based in part on the agency's belief that small businesses are more likely to realize a benefit from this regulation because they are more likely to submit reports of minor changes as prior approval supplements. While we recognized that a few small firms may have to start submitting an annual report rather than a biennial supplement, we did not believe that this would impose a significant cost on small businesses. We received no comments on small business impacts that lead us to change this position. Therefore, the agency certifies that the rule will not have a significant effect on a substantial number of small entities.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (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.

Title: Supplements and Other Changes to Approved New Animal Drug Applications

Description: The FDA with this final rule is amending its regulations on supplements and other changes to an approved NADA or ANADA to implement the manufacturing changes provisions of section 506A of the act. Under § 514.8(b)(2), the regulation describes reporting requirements for submission and approval of a supplement prior to distribution of the drug made using the change (major change). Section 514.8(b)(3)(i) describes reporting requirements for submission of a supplement at least 30 days prior to distribution of the drug made using the change (moderate change). Section 514.8(b)(3)(vi) describes reporting requirements for a category of supplemental changes designated by the agency which allows the holder of an approved application to commence distribution of the drug involved upon receipt by the agency of a supplement for the change. Section 514.8(b)(4)(iii) provides requirements for changes and updated stability data to be submitted in an annual report (minor changes). Section 514.8(c)(2)(ii) describes reporting requirements for labeling and other changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major change). Section 514.8 (c)(3)(iii) provides reporting requirements for labeling changes to be placed in effect prior to receipt of written notice of approval of a supplemental application, and § 514.8(c)(4) describes reporting

requirements for changes providing for additional distributors to be reported under § 514.80, records and reports concerning experience with approved new animal drugs.

Description of Respondents: Sponsors of new animal drug applications.

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 Respondent	Total Annual Responses	Hours per Response	Total Hours
514.8(b)(2)	40	5.9	234	100	23,400
514.8(b)(3)(i)	40	5.0	200	40	8,000
514.8(b)(3)(vi)	40	3.6	145	40	5,800
514.8(b)(4)(iii)	40	15.2	609	40	24,360
514.8(c)(2)(ii)	40	0.3	10	100	1,000
514.8(c)(3)(iii)	40	0.5	20	40	800
514.8(c)(4)	40	0.3	10	20	200
Total					63,560

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

FDA announced that the proposed rule contained information collection provisions that were subject to review by OMB under the Paperwork Reduction Act of 1995 and invited public comment (64 FR 53281). In response to that notice, FDA did not receive any comments regarding the information collection requirements contained in the final rule. However, with the use of improved technology, CVM performed a retrospective burden analysis resulting in an adjustment to the previous burden table that was published in the October 1, 1999, **Federal Register**. CVM examined fiscal year 2003 data for its analysis and using CVM's database, for tracking submissions including supplements to NADAs and ANDAs, was able to determine the number of respondents and the types and number of supplements submitted that year. The number of respondents (40) is the approximate number of sponsors of New Animal Drug Applications and Abbreviated New Animal Drug Applications that submitted supplemental applications. This number was determined by using a

retrospective analysis of supplements actually received by CVM for fiscal year 2003. The number of responses per respondent was obtained by dividing the "Total Annual Responses" by the "Number of Respondents." The "Total Annual Responses" are the actual manufacturing supplement numbers, i.e., completed submissions for the analysis year (fiscal year 2003).

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order, and, consequently, a federalism summary impact statement is not required.

X. References

The following reference has been placed on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Eastern Research Group, *Pharmaceutical Industry Cost Savings Through Use of the Scale-Up and Post-Approval Guidance for Immediate Release Solid Oral Dosage Forms (SUPAC-IR)*, January 7, 1998, Contract Number 223-94-8031, page 8.

List of Subjects

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, Polychlorinated biphenyls (PCB's).

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 delegated to the Commissioner of Food and Drugs, 21 CFR parts 25, 500, 514, and 558 are amended as follows:

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

■ 1. 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]

■ 2. Section 25.33 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

■ 3. 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]

■ 4. Section 500.25 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 514—NEW ANIMAL DRUG APPLICATIONS

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

Authority: 21 U.S.C. 321, 331, 351, 352, 356a, 360b, 371, 379e, 381.

■ 6. 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) *Assess the effects of the change* means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug as these factors may relate to the safety or effectiveness of the drug.

(ii) *Drug substance* means an active ingredient as defined under § 210.3(b)(7) of this chapter.

(iii) *Minor changes and stability report (MCSR)* means an annual report that is submitted to the application once each year within 60 days before or

after the anniversary date of the application's original approval or on a mutually agreed upon date. The report must include minor manufacturing and control changes made according to § 514.8(b)(4) or state that no changes were made; and stability data generated on commercial or production batches according to an approved stability protocol or commitment.

(iv) *Specification* means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drugs including, for example, drug substances, Type A medicated articles, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug. For the purpose of this definition, the term "acceptance criteria" means numerical limits, ranges, or other criteria for the tests described.

(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 by inclusion of the information in the annual report to the application under paragraph (b)(4) of this section.

(ii) The holder of an approved application under section 512 of the act must assess the effects of the change 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 drug, or by notification in the next annual report described in paragraph (b)(4) of this section).

(iv) In each supplement and amendment to a supplement providing for a change under paragraph (b)(2) or (b)(3) of this section, the applicant must include a statement certifying that a field copy has been provided to the appropriate FDA district office. No field copy is required for a supplement providing for a change made to a drug manufactured outside of the United States.

(v) 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. For supplements, this list must be provided in the cover letter.

(2) *Changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major changes).* (i) A supplement must be submitted for any change in the drug, 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 drug as these factors may relate to the safety or effectiveness of the drug.

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

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

(B) Changes requiring completion of appropriate clinical studies to demonstrate the equivalence of the drug to the drug as manufactured without the change;

(C) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug 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 drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(E) Changes in a drug product container closure system that controls the drug delivered to the animal or changes in the type or composition of a packaging component that may affect the impurity profile of the drug product;

(F) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance 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;

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

(iii) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug made using a change under paragraph (b)(2) of this section. The supplement must be labeled "Prior Approval Supplement."

Except for submissions under paragraph (b)(2)(v) of this section, the following information must be contained in the supplement:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The drug(s) involved;

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

(E) A description of the methods used and studies performed to assess the effects of the change;

(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, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and standard operating procedures 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 related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(2)(iii)(E) and (b)(2)(iii)(F) of this section; and

(J) Any other information as directed by FDA.

(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 must be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(v) *Comparability Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of the drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect. A comparability protocol supplement must be labeled "Prior Approval Supplement—Comparability Protocol."

(3) *Changes requiring submission of a supplement at least 30 days prior to distribution of the drug made using the change (moderate changes).* (i) A supplement must be submitted for any change in the drug, 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 drug as these factors may relate to the safety or effectiveness of the drug.

(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 drug except as otherwise described in paragraphs (b)(2) and (b)(4) of this section;

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

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

(*2*) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(C) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(iii) A supplement submitted under paragraph (b)(3)(i) or (b)(3)(vi) 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 made. The supplement submitted under paragraph (b)(3)(i) 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 drug made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(2)(iii)(A) through (b)(2)(iii)(J) of this section must be contained in the supplement.

(v) The applicant must not distribute the drug 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 drug 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. In this case, the applicant must not distribute the drug made

using the change until the supplement has been amended to provide the missing information.

(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 involved upon receipt by the agency of a supplement for the change. The information listed in paragraphs (b)(2)(iii)(A) through (b)(2)(iii)(J) 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 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 drug product or from one container closure system to another.

(vii) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug(s) 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 drug, 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 drug as these factors may relate to the safety or effectiveness of the drug must be documented by the applicant in an annual report to the application as

described under paragraph (a)(2)(iii) of this section. The report must be labeled "Minor Changes and Stability Report."

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

(A) Any change made to comply with a change to an official compendium, except a change in paragraph (b)(3)(ii)(C) of this section, that is consistent with FDA statutory and regulatory requirements;

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

(C) Replacement of equipment with that of the same design and operating principles except for those equipment changes described in paragraph (b)(3)(ii)(B)(2) of this section;

(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 drug product, without a change from one container closure system to another;

(E) A change within the container closure system for a nonsterile drug product, based upon a 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 production batches obtained from a protocol approved in the application;

(G) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the drug being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure; 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) A completed Form FDA 356V;

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

(C) A detailed description of the change(s);

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

(E) The date each change was implemented;

(F) Data from studies and tests performed to assess the effects of the change;

(G) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, relevant validation protocols and/or standard operating procedures;

(H) 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;

(I) Updated stability data generated on commercial or production batches according to an approved stability protocol or commitment; and

(J) Any other information as directed by FDA.

(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 drug made using the change (major changes).* (i) Addition of intended uses and changes to package labeling require a supplement. These changes include, but are not limited to:

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

(B) Addition of an intended use;

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

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

(*2*) Any other parts of the 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)(5)(ii).

(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 drug. The supplement must contain the following:

(A) A completed Form FDA 356V;

(B) A detailed description of the proposed change;

(C) The drug(s) involved;

(D) The data derived from studies in support of the change; and

(E) 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 drug safety proposed in supplemental applications must be placed into effect immediately:

(A) The addition to package labeling, promotional labeling, or prescription drug advertising of additional warning, contraindication, adverse reaction, 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 drug 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—Labeling Changes Being Effected";

(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 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 and the drug is being distributed with the proposed labeling, FDA may initiate an enforcement action because the drug is misbranded under section 502 of the act and/or adulterated under section 501 of the act. In addition, under section 512(e) of the act, FDA may, after due notice and opportunity for a hearing, issue an order withdrawing approval of the application.

(4) *Changes providing for additional distributors to be reported under Records and reports concerning experience with approved new animal drugs (§ 514.80).* 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 or abbreviated new animal drug application if the conditions described under § 514.80(b)(5)(iii) are met.

(d) *Patent information.* The applicant must 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 drug, the applicant must include such a statement.

(f) *Good laboratory practice for nonclinical laboratory studies.* A supplemental application that contains nonclinical laboratory studies must 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.

■ 7. Section 514.106 is amended by removing paragraphs (b)(1)(xiv), and 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)(*1*) through (c)(2)(i)(C)(*3*).

* * * * *

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

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

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

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

§ 558.5 [Amended]

■ 9. Section 558.5 is amended in paragraph (j) by removing "514.8(d) and (e)" and by adding in its place "514.8(c)(3)".

Dated: 9/1/06
September 1, 2006.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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