DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 2, 3, 5, 10, 12, 16, 20, 25, 50, 54, 56, 58, 60, 70, 71, 200, 201, 202, 206, 207, 210, 211, 299, 300, 310, 312, 314, 316, 320, 333, 369, 510, 514, 520, 522, 524, 529, 800, 801, 807, 809, 812, and 860

[Docket No. 98N–0720]

Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act; Confirmation of Effective Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule; confirmation of effective date.

SUMMARY: The Food and Drug Administration (FDA) published in the **Federal Register** of January 5, 1999 (64 FR 396), a direct final rule. The direct final rule amended FDA's regulations by removing references to the repealed statutory provision of the Federal Food, Drug, and Cosmetic Act (the act) under which the agency certified antibiotic drugs. The direct final rule also removed references to the repealed antibiotic monograph regulations and to those regulations dealing with antibiotic applications. This document confirms the effective date of the direct final rule.

EFFECTIVE DATE: The effective date of the direct final rule published at 64 FR 396 is confirmed as May 20, 1999.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION: FDA solicited comments concerning the direct final rule for a 75-day period ending March 22, 1999. FDA stated that the effective date of the direct final rule would be on May 20, 1999, 60 days after the end of the comment period, unless any significant adverse comment was submitted to FDA during the comment period. FDA did not receive any significant adverse comments.

Therefore, under the act, the FDA Modernization Act, and authority delegated to the Commissioner of Food and Drugs, notice is given that no objections were filed in response to the January 5, 1999, final rule. Accordingly, the amendments issued thereby are effective May 20, 1999.

Dated: May 10, 1999.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 99–12230 Filed 5–14–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 315 and 601

[Docket No. 98N–0040]

RIN 0910–AB52

Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations on the evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis and monitoring of diseases. FDA is issuing these regulations in accordance with the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). These regulations are intended to clarify existing regulations applicable to the approval of radiopharmaceutical drugs and biologics under the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act (the PHS Act).

EFFECTIVE DATE: Effective July 16, 1999.

FOR FURTHER INFORMATION CONTACT: Patricia Y. Love, Center for Drug Evaluation and Research (HFD–160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7510; or George Q. Mills, Center for Biologics Evaluation and Research (HFM–573), 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–5097.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 22, 1998 (63 FR 28301), FDA published a proposed rule to implement section 122 of the Modernization Act (Pub. L. 105–115). Section 122(a)(1) of the Modernization Act directs FDA to issue proposed and final regulations on the approval of radiopharmaceuticals intended for use in diagnosing or monitoring a disease or a manifestation of disease in humans. The proposed regulations apply to the approval of in vivo radiopharmaceuticals (both drugs and biologics) used for diagnosis and monitoring.

The preamble to the proposed rule noted that FDA was in the process of revising and supplementing its guidance to industry on product approval and other matters related to the regulation of diagnostic radiopharmaceutical drugs and biologics, and stated that such guidance would address the application of the proposed rule. In the **Federal Register** of October 14, 1998 (63 FR 55067), FDA announced the availability of a draft guidance for industry entitled ''Developing Medical Imaging Drugs and Biologics'' (medical imaging draft guidance). The guidance, when completed, will assist developers of drug and biological products used for medical imaging, including radiopharmaceuticals used in disease diagnosis, in planning and coordinating the clinical investigations of, and submitting various types of applications for, such products. The guidance will also provide information on how the agency will interpret and apply provisions in the final rule on diagnostic radiopharmaceuticals.

In the **Federal Register** of January 5, 1999 (64 FR 457), FDA reopened until February 12, 1999, the comment period on the medical imaging draft guidance. In the **Federal Register** of February 16, 1999 (64 FR 7561), the agency further extended the comment period to April 14, 1999.

Several of the comments on the proposed rule on diagnostic radiopharmaceuticals addressed issues that are also relevant to the medical imaging draft guidance. In FDA's responses to the comments set forth in section III of this document, the agency refers to relevant portions of the draft guidance that interpret and apply provisions of the regulations on diagnostic radiopharmaceuticals. In finalizing the medical imaging guidance, FDA will carefully consider all comments received on the proposed rule that are relevant to issues addressed in the draft guidance.

II. Highlights of the Final Rule

In accordance with section 122 of the Modernization Act, the final rule adds new regulations pertaining to the review and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring. The new regulations in part 315 (21 CFR part 315) and part 601 (21 CFR part 601) (§§ 601.30 through 601.35)) complement and clarify existing regulations on the approval of drugs and biologics in part 314 (21 CFR part 314) and part 601, respectively. The regulations include a definition of diagnostic radiopharmaceuticals and

provisions that address the following aspects of these products: (1) General factors to be considered in determining safety and effectiveness, (2) proposed indications for use, (3) evaluation of effectiveness, and (4) evaluation of safety.

FDA revised the proposed rule in response to comments received on the proposal. Proposed §§ 315.4(b) and 601.33(b) were revised to clarify that where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

FDA also revised the provisions on the evaluation of effectiveness of a diagnostic radiopharmaceutical. The agency revised proposed §§ 315.5(a)(1) and (a)(2) and 601.34(a)(1) and (a)(2) to state that claims of structure delineation and of functional, physiological, or biochemical assessment must be demonstrated in a defined clinical setting that is appropriate for the intended clinical benefit (as is the case with claims of: (1) Disease or pathology detection or assessment and (2) diagnostic or therapeutic patient management). In addition, FDA revised §§ 315.5(a)(1) and 601.34(a)(1) to state that a structure delineation claim involves an ability ''to locate anatomical structures and to characterize their anatomy,'' rather than an ability ''to locate and characterize normal anatomical structures.''

FDA also revised the provisions on the evaluation of the safety of a diagnostic radiopharmaceutical. Proposed §§ 315.6(a) and 601.35(a) were revised to add to the factors that FDA will consider in assessing the safety of a diagnostic radiopharmaceutical the results of any previous human experience with the carrier or ligand of a radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product. Similarly, the agency revised §§ 315.6(c)(2) and 601.35(c)(2) to specify that the amount of new safety data required to be submitted for a particular diagnostic radiopharmaceutical will depend on the characteristics of the product and available information on the safety of not only the diagnostic radiopharmaceutical itself but also its carrier or ligand. These sections were also revised to state that the safety information that FDA may require may include the results of clinical studies, in addition to the results of preclinical studies. Additionally, these sections were revised to clarify that the agency will establish categories of diagnostic radiopharmaceuticals based on defined risk characteristics and, upon reviewing a particular diagnostic radiopharmaceutical's relevant product characteristics and safety information, will place the radiopharmaceutical into the appropriate safety risk category. FDA also deleted the requirements in proposed §§ 315.6(d) and 601.35(d) on the tests that must be included in a radiation dosimetry evaluation of a diagnostic radiopharmaceutical (i.e., dosimetry to total body, to specific organs or tissues, and, as appropriate, to target organs or tissues) in favor of addressing this matter in the medical imaging guidance.

Finally, FDA made minor editorial changes to the final rule in response to the President's June 1, 1998, memorandum on plain language in government writing.

III. Responses to Comments on the Proposed Rule

FDA received nine written comments on the proposed rule. The comments were submitted by manufacturers, trade associations, universities, and a health care organization.

A. General Responses

1. One comment expressed support for the intent of the proposed regulations, but it questioned how FDA could develop acceptable indications, as well as safety and effectiveness criteria for radiopharmaceuticals, without doing the same for all diagnostic drugs and biologics. The comment maintained that while radiopharmaceuticals may be a unique ''chemical'' class, they are part of the ''therapeutic'' class of diagnostic agents used for medical imaging. The comment further contended that because the proposed regulations on diagnostic radiopharmaceuticals were designed to clarify FDA's expectations and might reduce the cost of developing these products, adoption of these regulations would create a competitive disadvantage for companies developing nonradiopharmaceutical products for the same indications and efficacy endpoints.

Section 122(a)(1) of the Modernization Act directs FDA to develop regulations specifically governing the approval of diagnostic radiopharmaceuticals. It does not direct the agency to establish new approval procedures that would apply to all in vivo diagnostic agents, including radiopharmaceuticals and contrast agents. Consequently, as stated in §§ 315.1 and 601.30, the final rule applies to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use; it does not apply to radiopharmaceuticals intended for therapeutic use or to nonradiopharmaceutical products. FDA will consider whether it should develop similar regulations for nonradiopharmaceutical diagnostic agents in the future.

However, FDA agrees with the comment that there are common principles in developing diagnostic imaging products. FDA's medical imaging draft guidance addresses such matters as conducting clinical studies and submitting applications for all medical imaging drugs and biologics, not just diagnostic radiopharmaceuticals. In doing so, the draft guidance elaborates on the concepts set forth in the proposed rule on diagnostic radiopharmaceuticals. Consequently, although the final rule applies only to diagnostic radiopharmaceuticals, FDA is proposing in the medical imaging draft guidance that the principles set forth in this final rule should apply to all medical imaging drugs and biologics, including contrast agents.

B. Definition

Proposed §§ 315.2 and 601.31 defined a diagnostic radiopharmaceutical as an article that is intended for use in the diagnosis or monitoring of a human disease or manifestation of disease and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. The definition also included any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a previously defined article.

2. One comment, noting that three of the four indication categories under proposed §§ 315.4 and 601.33 did not include the word ''diagnostic,'' asked whether the regulations should state a definition of ''radiopharmaceutical'' rather than ''diagnostic radiopharmaceutical'' to be consistent with section 122 of the Modernization Act.

Although section 122(b) of the Modernization Act includes a definition of ''radiopharmaceutical'' rather than ''diagnostic radiopharmaceutical,'' the term applies only to radiopharmaceuticals ''intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans * * *.'' Consequently, FDA states in §§ 315.1 and 601.30 that the regulations in part 315 and part 601, subpart D, respectively, apply to radiopharmaceuticals intended for diagnostic and monitoring use and not to radiopharmaceuticals intended for therapeutic purposes. FDA believes that

the definition and use of the term ''diagnostic radiopharmaceutical'' in these regulations are consistent with the Modernization Act and the scope of these regulations. Although three of the four categories of indications do not include the word ''diagnostic,'' it is clear from the context of the regulations that each of the categories applies to diagnostic or monitoring indications and not to therapeutic indications.

3. Two comments asked that FDA clarify a statement in the preamble to the proposed rule (63 FR 28301 at 28303) that the definition of diagnostic radiopharmaceutical includes articles that exhibit spontaneous disintegration leading to reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons.

Proposed §§ 315.2 and 601.31 defined a diagnostic radiopharmaceutical as an article ''that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons * * *.'' This definition is identical to the definition of ''radiopharmaceutical'' in section 122(b) of the Modernization Act. FDA was concerned that this definition might be interpreted as excluding an article that exhibits spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons (i.e., the electron capture process of decay). Therefore, the agency stated in the preamble that it interprets the definition of ''radiopharmaceutical'' in section 122(b) of the Modernization Act and ''diagnostic radiopharmaceutical'' in proposed §§ 315.2 and 601.31 as including such an article. This statement was intended to clarify that diagnostic radiopharmaceuticals include articles with unstable nuclei that do not initiate decay by spontaneous disintegration but by spontaneous incorporation of an electron into the nucleus, bonding with a proton to form a neutron. This is followed by neutrino emission from the nucleus and both x-ray and Auger electron emissions from the electron shells. Iodine-123 is an example of a radionuclide that decays in this manner.

C. Indications

Proposed §§ 315.4(a) and 601.33(a) specified the following categories of indications for which FDA may approve a diagnostic radiopharmaceutical: (1) Structure delineation; (2) functional, physiological, or biochemical assessment; (3) disease or pathology detection or assessment; and (4) diagnostic or therapeutic patient management.

4. One comment, referring to examples of structural delineation and functional/physiological/biochemical assessment indications provided in the preamble to the proposed rule, requested that FDA provide examples of actual claim language and primary endpoints of adequate and well controlled clinical trials for drugs with such types of indications.

FDA does not believe that it would be appropriate to suggest potential language for indications for use or primary clinical endpoints outside of the context of evaluating a specific diagnostic radiopharmaceutical for a desired indication. However, the medical imaging draft guidance provides examples of products with such categories of indications and discusses the kinds of claim statements that may be permitted in promotional materials for such products. The draft guidance also provides examples of the types of endpoints that are appropriate for clinical studies on medical imaging drugs and biologics.

5. One comment stated that the distinction between the disease detection and patient management categories of indications in proposed §§ 315.4(a)(3) and (a)(4) and 601.33(a)(3) and (a)(4) was vague and asked whether the former category allowed for use of the phrase ''as an aid in the diagnosis of [a specific disease].'' The comment further stated that the difference between the two categories appeared to be related to the ability to provide diagnostic information and/or lead to a decision on patient management. However, the comment found it difficult to understand how a diagnostic radiopharmaceutical could characterize a specific disease as described in the preamble (63 FR 28301 at 28303) and not be of diagnostic value (i.e., fall within the diagnostic or therapeutic patient management indication category).

FDA agrees that there is a need to further clarify the distinction between the disease or pathology detection and assessment indication category and the diagnostic or therapeutic patient management indication category. A disease or pathology detection or assessment claim is established by demonstrating that a diagnostic radiopharmaceutical provides clinically useful information that can assist in the detection, localization, or characterization of a specific disease or pathological state in a defined clinical setting. However, the way that the information affects patient management is implied and may not be directly studied. The phrases ''as an aid in'' or ''as an adjunct to'' may be appropriate for this type of indication. On the other hand, a diagnostic or therapeutic patient management claim is established by explicitly demonstrating a radiopharmaceutical's ability to provide imaging or related information that leads directly to an appropriate diagnostic or therapeutic management decision for patients in a defined clinical setting. FDA will revise the medical imaging draft guidance to further distinguish disease/pathology detection and assessment indications from patient management indications.

6. One comment, stating that reliance on patient management for a diagnostic claim might be unfounded, asked what indication language FDA might approve for a diagnostic radiopharmaceutical if there were no approved therapy for treating a specific disease.

A diagnostic or patient management decision need not necessarily relate to the use of an approved drug product or therapy. Therefore, the absence of an approved therapy for a particular disease would not necessarily mean that FDA would not approve a diagnostic radiopharmaceutical with an indication for diagnostic or therapeutic management of patients with that disease. However, the applicant would need to demonstrate that its product has some clinical value. For example, in a situation in which two disorders are difficult to distinguish but a treatment exists for only one of the two, a radiopharmaceutical might be used to distinguish between the two disorders, thereby directly affecting subsequent patient management. In addition, a diagnostic radiopharmaceutical could have clinical usefulness in providing disease progression information about an untreatable disease; a patient management claim might be appropriate if such information were shown to directly affect some aspect of patient management (e.g., symptomatic treatment, avoidance of unnecessary treatment). As with all diagnostic radiopharmaceuticals for which a patient management indication is sought, FDA would need to determine whether the proposed clinical studies on the product included endpoints for assessing the appropriateness of patient management or clinical outcomes. The medical imaging draft guidance provides further clarification on the indications that may be appropriate for a diagnostic radiopharmaceutical under these circumstances.

7. Two comments expressed concern that FDA might narrowly interpret the diagnostic or therapeutic patient management indication category, noting that the two examples provided in the preamble involved indications dealing

with initial patient management, i.e., deciding therapeutic course. The comments sought confirmation that this indication category would include diagnostic radiopharmaceuticals used in followup patient management, i.e., monitoring response to therapy.

Although the two examples in the proposed rule related to initial patient management rather than monitoring response to therapy, FDA affirms that the diagnostic or therapeutic patient management indication category includes drugs used to monitor patient response to therapy if the response to therapy has direct implications for subsequent patient management. Possible diagnostic or therapeutic patient management indications might include diagnostic evaluation, use of a nonregulated therapy such as surgery, and other significant aspects of how a patient is treated. For example, a diagnostic radiopharmaceutical might be used to evaluate whether therapy for a malignancy is causing tumor regression if that information directly affects subsequent patient management decisions. A patient management indication also might be appropriate for a radiopharmaceutical that provides a convenient, well tolerated, accurate test that has been shown to effectively replace a more cumbersome or risky standard battery of tests, regardless of the availability of therapy.

8. Proposed §§ 315.4(b) and 601.33(b) stated that where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use might refer to a process or to more than one disease or condition. One comment stated that this provision properly implements the special rule in section 122(a)(2) of the Modernization Act that a radiopharmaceutical may be approved for indications referring to manifestations of disease (such as biochemical, physiological, anatomical, or pathological processes) common to, or present in, one or more disease states. However, the comment asked that the phrase ''biochemical, physiological, anatomical, or pathological'' be added before the word ''process'' to eliminate the possibility that ''process'' might be construed as referring to a diagnostic procedure.

FDA agrees with the comment and has revised §§ 315.4(b) and 601.33(b) accordingly.

D. Evaluation of Effectiveness

In proposed §§ 315.5 and 601.34, FDA set forth the specific criteria that the agency would use to evaluate the effectiveness of a diagnostic radiopharmaceutical. The proposed rule stated that effectiveness would be assessed by evaluating the ability of the diagnostic radiopharmaceutical to provide useful clinical information related to the proposed indications for use. The method of this evaluation would vary depending on the proposed indication.

9. One comment maintained that the proposed rule should have detailed the differences between diagnostic radiopharmaceuticals and conventional, nonradioactive drugs as a basis for a different regulatory treatment. For example, the comment stated that adequate and well controlled investigations are not applicable to diagnostic radiopharmaceuticals and that specific studies involving each potentially applicable disease state should not be required for such drugs. The comment argued that ''proof of principle'' is all that has been required by the Atomic Energy Commission (AEC) and that use of this standard would be a good way to implement the requirements of the Modernization Act.

Section 122(a)(1)(A) of the Modernization Act directs FDA to develop regulations for determining the safety and effectiveness of diagnostic radiopharmaceuticals under section 505 of the act (21 U.S.C. 355) and section 351 of the PHS Act (42 U.S.C. 262); it does not exempt diagnostic radiopharmaceuticals from the requirements of those statutory provisions. Under section 505(d)(5) of the act, FDA may refuse to approve a new drug application (NDA) if, among other things, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use in its proposed labeling. ''Substantial evidence'' is defined as adequate and well controlled investigations, including clinical investigations, by qualified experts, on the basis of which such experts may fairly and responsibly conclude that the drug will have its intended effect. Under section 351 of the PHS Act, FDA approves a biologics license application (BLA) on, among other things, a demonstration that the biological product is safe, pure, and potent. Potency has long been interpreted to include effectiveness ''as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended'' (21 CFR 600.3(s)). FDA believes that the standard of substantial evidence is appropriate for use in evaluating the sufficiency of evidence of effectiveness submitted in a BLA (see FDA's guidance for industry entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,'' May 1998). For these reasons, FDA may not establish regulations for diagnostic radiopharmaceuticals that exempt such drugs and biologics from the statutory requirements.

The ''proof of principle'' concept noted by the comment was used by the Nuclear Regulatory Commission (NRC), the successor agency to the AEC. The NRC licenses persons who use nuclear materials. NRC standards are directed exclusively at radiological health and safety. The NRC focuses on ensuring an adequate level of radiation protection without regard to whether a radiopharmaceutical actually works. Because it is FDA's statutory responsibility to determine the safety and effectiveness of drug products, the NRC's standards are not relevant to the approval of diagnostic radiopharmaceuticals under the act. Proof of principle, e.g., the metabolic, pharmacokinetic, and pharmacological database on a diagnostic radiopharmaceutical, is only part of the drug development process. This information alone is insufficient to meet the requirements in the act and in FDA regulations on safety and effectiveness and on product labeling statements regarding such matters as safe use, the adverse event profile, and clinical use information.

10. One comment maintained that because statements in the preamble describing the structure delineation and functional/physiological/biochemical assessment indication categories do not mention clinical benefit, unlike the descriptions of the other two categories, FDA should state that a demonstration of ''traditional'' clinical utility or benefit is not required for diagnostic radiopharmaceuticals with these types of indications. However, the comment noted that this interpretation contradicted the statement in proposed §§ 315.5(a) and 601.34(a) that the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide ''useful clinical information'' concerning its proposed indications. The comment stated that it was unclear how one could provide useful clinical information related to a proposed indication for use that would not be of diagnostic or patient management value. Alternatively, the comment asked that FDA provide an example of a drug that demonstrates clinical utility but does not aid in diagnosis or contribute to patient management.

Although not explicitly stated in the preamble discussion on indication categories, a demonstration of clinical

benefit, i.e., ability to provide useful clinical information related to proposed indications for use, is required for approval of all types of diagnostic radiopharmaceuticals under §§ 315.5(a) and 601.34(a). The indication categories are intended to describe the types of clinically useful information that could be derived from an imaging study, and the type of indication for a particular product is related to the type of clinical trial designs that are used in the clinical studies. The draft medical imaging guidance further addresses these matters.

It is indeed possible for a diagnostic radiopharmaceutical to provide useful clinical information without directly being effective for detecting or assessing a disease or aiding patient management. For example, a diagnostic radiopharmaceutical might be used to locate and outline a normal parathyroid gland; while this information might not directly result in disease diagnosis and might not be demonstrated to improve patient management, it could indirectly assist a physician in planning and performing surgery to remove a mass in the thyroid gland.

11. Proposed §§ 315.5(a)(1) through (a)(5) and 601.34(a)(1) through (a)(5) set forth the criteria for demonstrating effectiveness with respect to particular categories of indications. A structure delineation claim would be established by demonstrating the ability of the diagnostic radiopharmaceutical to locate and characterize normal anatomical structures. A claim of functional, physiological, or biochemical assessment would be established by demonstrating reliable measurement of functions or physiological, biochemical, or molecular processes. A claim of disease or pathology detection or assessment would be established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing a disease or pathology. A claim of diagnostic or therapeutic patient management would be established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic management of patients.

One comment suggested that the word ''normal'' be deleted from proposed §§ 315.5(a)(1) and 601.34(a)(1) because radiopharmaceuticals with structure delineation indications are used to locate and characterize structures that may be normal or abnormal, and in some cases they may be used to help determine the abnormal appearance of a structure.

FDA agrees to delete the word ''normal'' from §§ 315.5(a)(1) and 601.34(a)(1) because a structure delineation claim may be appropriate for a diagnostic radiopharmaceutical that is used to determine the anatomical appearance of a structure even when the anatomy is abnormal. However, to clarify FDA's intent as to what is needed to demonstrate a structure delineation claim, the agency is further revising these provisions to state that a claim of structure delineation is established by demonstrating the ability to locate anatomical structures and to characterize their anatomy. FDA recognizes the need to clarify when a structure delineation claim is appropriate rather than a claim in one of the other indication categories. The agency will consider revising the medical imaging draft guidance to further explain the scope of permissible structure delineation claims.

12. One comment maintained that the information provided by radiopharmaceuticals with functional, physiological, or biochemical assessment indications may be either quantitative, semiquantitative, or qualitative. To prevent §§ 315.5(a)(2) and 601.34(a)(2) from being interpreted as permitting only quantitative measurement of function or process in establishing a functional, physiological, or biochemical assessment claim, the comment requested that the phrase ''quantitative, semi-quantitative, or qualitative'' be added before the word ''measurement.''

FDA agrees with the comment that a diagnostic radiopharmaceutical with a functional, physiological, or biochemical assessment indication may be established through either a quantitative, semi-quantitative, or qualitative measurement of a function or process. However, the agency concludes that it is not necessary to revise §§ 315.5(a)(2) and 601.34(a)(2) as requested because these provisions do not require any specific type of measurement.

13. One comment asked FDA to confirm that claims involving structure delineation or physiological assessment would not require evaluation in a defined clinical setting under proposed §§ 315.5(a)(1) and (a)(2) and 601.34(a)(1) and (a)(2), as would be required for disease detection and patient management claims under proposed §§ 315.5(a)(3) and (a)(4) and 601.34(a)(3) and (a)(4). In particular, the comment asked whether, if a sponsor could demonstrate unequivocally a diagnostic radiopharmaceutical's ability to quantitate nucleic acid synthesis (one of the preamble's examples of a biochemical assessment indication), FDA would require the sponsor to demonstrate such effectiveness in a clinically relevant setting or patient population.

FDA believes that to demonstrate that a diagnostic radiopharmaceutical has the ability to provide useful clinical information in accordance with §§ 315.5(a) and 601.34(a), the drug must be evaluated in a defined clinical setting, regardless of its proposed indication. Consequently, FDA has revised §§ 315.5(a)(1) and (a)(2) and 601.34(a)(1) and (a)(2) to specify that structure delineation and functional, physiological, or biochemical assessment claims, like disease detection and patient management claims, must be demonstrated in a defined clinical setting. The medical imaging draft guidance provides further discussion and explanation of the defined clinical setting. Claims involving structure delineation or physiological assessment must be evaluated under a clinical protocol and require a population from a clinically relevant setting. Regarding the hypothetical situation posed by the comment, even if a sponsor were able to demonstrate unequivocally that a diagnostic radiopharmaceutical was able to quantitate nucleic acid synthesis, the sponsor would have to demonstrate the usefulness of the imaging information in a clinically relevant setting. The clinical setting might be broad, demonstrating the common value of nucleic acid synthesis. Alternatively, the clinical studies might involve patients with a need for a particular type of evaluation (e.g., radionuclide ejection fraction) regardless of the underlying disease.

14. Under proposed §§ 315.5(b) and 601.34(b), the accuracy and usefulness of diagnostic information provided by a diagnostic radiopharmaceutical would be determined by comparison with a reliable assessment of actual clinical status, which could be provided by a diagnostic standard or standards of demonstrated accuracy. One comment maintained that these sections should be deleted because the act does not require either accuracy or usefulness. The comment stated that practitioners determine the accuracy and usefulness of a diagnostic radiopharmaceutical and that this information may be found in peer-reviewed literature, in the United States Pharmacopoeia Drug Information, and at professional and continuing medical education meetings. The comment added that accuracy and usefulness were never a part of the AEC process.

FDA declines the request to delete §§ 315.5(b) and 601.34(b). Although section 505(d) of the act and section 351 of the PHS Act do not specifically require that a new drug or biologic be shown to be ''accurate'' and ''useful,'' they do authorize FDA, as noted previously, to refuse to approve an application if there is a lack of substantial evidence that the product will have the effect it purports or is represented to have under the proposed conditions of use, based on an evaluation of well controlled clinical trials on the product. The statistical assessment of such trials includes accuracy; the clinical assessment considers the usefulness of the diagnostic information in the studied clinical setting and the proposed indication. FDA acknowledges that in the practice of medicine physicians may obtain information about a particular diagnostic radiopharmaceutical from numerous sources, including the published literature, and they may make diagnosis and treatment decisions on the basis of such information. Such literature typically becomes available after a product is marketed. However, a diagnostic radiopharmaceutical may not be marketed unless the agency determines, on the basis of data from clinical trials and other information, that the drug is safe and effective under section 505 of the act or section 351 of the PHS Act, and that determination must include the accuracy and usefulness of the product.

E. Evaluation of Safety

Proposed §§ 315.6(a) and 601.35(a) listed the factors that FDA would consider in assessing the safety of a diagnostic radiopharmaceutical. These factors include the following: The radiation dose; the pharmacology and toxicology of the radiopharmaceutical (including any radionuclide, carrier, or ligand); the risks of an incorrect diagnostic determination; the drug's adverse reaction profile; and results of human experience with the drug for other uses.

15. One comment maintained that there is no ''pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand,'' as stated in proposed §§ 315.6(a) and 601.35(a).

FDA disagrees with the comment. The agency is aware of specific diagnostic radiopharmaceuticals, ligands, and carriers that have been shown to have a pharmacological or toxicological effect on the human body. For example, biological antibodies used in radiopharmaceuticals have demonstrated pharmacological and immunologic activity. In addition, as the development of radiopharmaceuticals increasingly focuses on receptors and metabolic processes, ligands (either synthesized peptides or antibodies) could have agonist or antagonist activity at nanomolar levels.

16. One comment asked why the safety of a diagnostic radiopharmaceutical might relate to the pharmacological action of its ligand rather than an observed adverse event, suggesting that a deleterious pharmacological action would be manifested as an adverse event.

The pharmacological action of a diagnostic radiopharmaceutical's ligand directly affects the sponsor's plan for detecting adverse events associated with the administration of a radiopharmaceutical. Without knowledge of the pharmacological action, the sponsor's selected time intervals for monitoring (e.g., immediate reactions, 7- to 10-day reactions, 3- to 6-month reactions) may not allow for observation, detection, and reporting of adverse events that occur during other time intervals. Also, some adverse events are not reported by patients and may not be suggested by animal studies; they may be identified only by physical examination (e.g., detection of nystagmus by cranial nerve examination). In addition, if the pharmacological action of the ligand is not known, the sponsor may not determine and use the appropriate modality (e.g., clinical evaluation, laboratory assessment, radiographic imaging) to monitor adverse events. For example, in a radiopharmaceutical that binds irreversibly to activated platelet receptors, a pharmacology evaluation would demonstrate an inhibition of platelet aggregation. Subsequent clinical studies should evaluate the bleeding time and potential drug interaction with treatments that prolong bleeding. Therefore, it is appropriate to include both the pharmacology and toxicology of a diagnostic radiopharmaceutical (including any radionuclide, carrier, or ligand) as well as the drug's adverse reaction profile as separate factors to consider in evaluating the safety of a diagnostic radiopharmaceutical.

17. One comment stated that FDA should delete the risks of an incorrect diagnostic determination as a factor in assessing the safety of a diagnostic radiopharmaceutical. The comment maintained that such risks depend on physician competence, patient cooperation, equipment quality, and other factors that are not characteristics of a diagnostic radiopharmaceutical, and that such a provision does not appear in the act.

FDA disagrees with the proposed deletion. The risk of an incorrect diagnostic determination is an independent factor to be considered in evaluating the safety of a diagnostic radiopharmaceutical under section 505 of the act or section 351 of the PHS Act. For example, a new diagnostic radiopharmaceutical might produce images and clinical information that require additional physician knowledge and competence for adequate interpretation or that might suggest an incorrect diagnosis even though interpreted by a well trained physician. Misinterpretation of the diagnostic images in such circumstances might pose a significant threat to the health of patients.

18. One comment stated that a diagnostic radiopharmaceutical's adverse reaction profile should not be considered because it is generally nonexistent, nonspecific, or trivial.

FDA disagrees with the comment. It is possible for a diagnostic radiopharmaceutical to have a specific and significant adverse reaction profile. Examples are the development of angina after the injection of a synthetic radiopharmaceutical to evaluate myocardial perfusion and the immune system response to the administration of a radiolabeled small peptide or antibody. The production of a human antimurine antibody has been demonstrated in response to both first administration as well as multiple administrations of a murine antibody. The production of the immune response to the administration of the murine antibody has elicited life-threatening anaphylactoid responses. Therefore, a diagnostic radiopharmaceutical's adverse reaction profile is a relevant factor to consider in assessing the drug's safety.

19. Two comments addressed the proposed safety assessment factor concerning ''the results of human experience with the radiopharmaceutical for other uses.'' One comment found this factor to be confusing and asked that FDA explain the phrase and provide some examples. Another comment agreed with the proposed rule that, when an applicant is seeking approval for a new indication for a previously approved radiopharmaceutical, the clinical data in the approved application and postmarketing experience with that product should be considered in assessing the safety of that radiopharmaceutical for the proposed new use. However, the comment maintained that human safety data on a

ligand or carrier used in a radiopharmaceutical may be important even though the radiopharmaceutical has not been previously approved. The comment stated that the radionuclide component of a radiopharmaceutical may have a long history of use in other radiopharmaceuticals and that most radiopharmaceutical issues (other than radiation dosimetry issues) will arise from the potential pharmacological or toxicological properties of the compound used in the carrier or ligand, about which there may be relevant safety information from use in marketed products. Therefore, the comment recommended that the following factor be added to the end of §§ 315.6(a) and 601.35(a):

> the results of previous human experience with the ligand or carrier component (if any) of the radiopharmaceutical where essentially the same chemical entity as the ligand or carrier has been used in a previously approved product (e.g., as the ligand or carrier in another diagnostic or therapeutic radiopharmaceutical or as the active ingredient in a nonradioactive product for therapeutic use).

FDA believes that human experience with a diagnostic radiopharmaceutical for previously approved uses (or even uses that have been studied but are unapproved) could provide important information about the safety of that radiopharmaceutical for a proposed new use. For example, the agency would review the safety experience of technetium-99m (Tc–99m) pyrophosphate used in bone imaging if a sponsor submitted an application for approval of that drug for a new indication, such as imaging of myocardial infarction. FDA agrees with the comment that the results of any human experience with the carrier or ligand of a diagnostic radiopharmaceutical, as used in a previously studied product (either as a ligand or carrier in a radiopharmaceutical or as an active ingredient in a nonradioactive drug product), should be considered in assessing the safety of a diagnostic radiopharmaceutical. Therefore, FDA has revised §§ 315.6(a) and 601.35(a) accordingly. However, the agency believes that this human experience must involve the exact chemical entity as the carrier or ligand of the diagnostic radiopharmaceutical undergoing safety assessment, rather than ''essentially the same chemical entity'' as the comment recommended. (For purposes of part 315 and subpart D of part 601, the terms ''carrier'' and ''ligand'' collectively refer to the entire nonradionuclidic portion of a diagnostic radiopharmaceutical.)

20. Proposed §§ 315.6(b) and 601.35(b) stated that the assessment of a diagnostic radiopharmaceutical's adverse reaction profile includes, but is not limited to, an evaluation of the potential of the drug (including its carrier or ligand) to elicit allergic or hypersensitivity responses, immunologic responses, changes in the physiologic or biochemical function of target and nontarget tissues, and clinically detectable signs or symptoms. One comment stated that although allergic and immunologic responses may be an issue with foreign proteins, a determination of antibody production in a small number of subjects would be enough to determine whether such responses are common.

FDA disagrees with the comment. The agency believes that there should be adequate clinical experience with a diagnostic radiopharmaceutical to identify uncommon as well as common allergic and immunologic responses to the radiopharmaceutical. Data on a small number of subjects generally are insufficient to identify an uncommon but potentially life-threatening adverse reaction.

21. One comment recommended adding the words ''Clinically significant'' before ''Changes in the physiologic or biochemical function of the target and nontarget tissues'' in proposed §§ 315.6(b)(3) and 601.35(b)(3) because such changes are relevant to assessing a diagnostic radiopharmaceutical's adverse reaction profile only when they are clinically significant. As an example, the comment stated that the process by which a radiopharmaceutical binds to an intended receptor on a cell surface might be regarded as a change in the biochemical function of the target tissue even though the change has no potential to adversely affect safety and has no other clinical significance. The comment contended that its suggested revision would be consistent with a statement in the agency's medical imaging draft guidance (i.e., that localization of a medical imaging drug in a target organ or tissue is not considered to have a biological effect unless it produces demonstrable perturbation).

FDA declines to revise §§ 315.6(b)(3) and 601.35(b)(3) as recommended. The agency believes that the potential of a product to change the physiologic or biochemical function of target and nontarget tissues should be evaluated. The clinical significance of any detected functional change should be assessed. If the functional change has little or no clinical significance, it likely will not affect the diagnostic radiopharmaceutical's adverse reaction profile.

22. One comment stated that the references to changes in the physiologic or biochemical function of target and nontarget tissues and to clinically detectable signs and symptoms should be deleted because such events do not occur (or not to any significant extent) with diagnostic radiopharmaceuticals.

FDA disagrees with the comment. FDA's experience with evaluating the safety of radiopharmaceuticals has demonstrated that the physiologic and biological function of target and nontarget tissues may be affected by the administration of a radiopharmaceutical. For example, as noted previously, the administration of a radiolabeled antibody can produce a strong immune system response. Moreover, changes in target and nontarget tissues can sometimes result in clinically detectable signs and symptoms, such as the anaphylactoid response discussed previously. Therefore, FDA may need information on a radiopharmaceutical's potential to produce changes in the physiologic or biochemical function of tissues as well as clinically detectable signs and symptoms to accurately assess the drug's adverse reaction profile.

23. Proposed §§ 315.6(c)(1) and 601.35(c)(1) stated that, among other information, FDA may require the following types of data to establish the safety of a diagnostic radiopharmaceutical: Pharmacology data, toxicology data, clinical adverse event data, and a radiation safety assessment. One comment maintained that pharmacology, toxicology, and clinical adverse event data are for the most part not relevant due to the minute mass of the radiopharmaceutical.

FDA disagrees with the comment. Diagnostic radiopharmaceuticals differ widely in mass, and the pharmacological and toxicological effects of a diagnostic radiopharmaceutical are not necessarily related to the mass of the drug product. However, the mass of a diagnostic radiopharmaceutical may be a relevant factor in FDA's determination of the type of pharmacology, toxicology, clinical adverse event monitoring, and radiation safety data needed to establish the safety of a diagnostic radiopharmaceutical.

24. Proposed §§ 315.6(c)(2) and 601.35(c)(2) stated that the amount of new safety data required for a diagnostic radiopharmaceutical would depend on the characteristics of the product and available information on the safety of the diagnostic radiopharmaceutical obtained from other studies and uses. Included among such information would be the dose, route of

administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of preclinical studies. FDA would categorize diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and would specify the amount and type of safety data appropriate for each category. For example, required safety data would be limited for a category of radiopharmaceuticals with a well established, low-risk profile.

One comment contended that these provisions fail to address the possibility of a reduction in required safety data for previously unapproved radiopharmaceuticals. The comment stated that where preexisting data demonstrate a history of safe use of a carrier or ligand of a diagnostic radiopharmaceutical, such information should permit a reduction in the amount of new safety data that the sponsor must provide. Therefore, the comment recommended that the phrase ''or its carrier or ligand component'' be added following ''radiopharmaceutical'' in §§ 315.6(c)(2) and 601.35(c)(2).

FDA agrees with the comment that such prior data may permit a reduction in the amount of new safety data that a sponsor may need to provide and has revised these sections accordingly.

25. One comment noted that ''results of preclinical studies,'' but not clinical studies, is listed among the kinds of information on the safety of a diagnostic radiopharmaceutical that might be used to determine the amount of new safety data required in an application. The comment argued that clinical information may also be important to consider in determining what new safety data is needed. Such clinical information could include data on a diagnostic radiopharmaceutical approved for a different indication, on a carrier or ligand that has a history of use as a carrier or ligand in an approved radiopharmaceutical or as the active ingredient in a therapeutic product, or from Phase 1 studies on the drug that is the subject of the pending application. Although the comment recognized that the list of information on the safety of a diagnostic radiopharmaceutical in proposed §§ 315.6(c)(2) and 601.35(c)(2) was not exclusive, the comment believed that failure to explicitly include the results of clinical studies might dissuade sponsors from providing FDA with useful clinical information early in the clinical development program for the drug.

FDA agrees with the comment and has revised these sections accordingly.

26. One comment agreed with FDA's proposal to define a category of low-risk radiopharmaceuticals that would be subject to reduced safety requirements. The comment stated that FDA should provide in a guidance document a description of the low-risk category, criteria for eligibility, and types of safety data required for products in this category. The comment contended that the medical imaging draft guidance does not specify the different safety requirements for Group 1 and Group 2 medical imaging drugs beyond stating that reduced safety monitoring is appropriate for Phase 2 and 3 studies on Group 1 drugs.

FDA agrees with the comment and will consider revising the medical imaging draft guidance to further address the type of safety information that may be appropriate for Group 1 and Group 2 medical imaging drugs.

27. One comment asked that proposed §§ 315.6(c)(2) and 601.35(c)(2) be revised to clarify that, even for radiopharmaceuticals that do not fall within a low-risk category, FDA will consider existing information and determine on an ad hoc basis the amount of new safety data that is required for a particular diagnostic radiopharmaceutical product.

FDA has revised §§ 315.6(c)(2) and 601.35(c)(2) to clarify the agency's approach to determining the amount of new safety data that will be required for a particular diagnostic radiopharmaceutical. As stated in revised §§ 315.6(c)(2) and 601.35(c)(2), FDA will consider certain product characteristics and available safety information obtained from other studies and uses in determining the amount of new safety information that is needed for each drug. The information that FDA may review includes, but is not limited to, the following: The dose, route of administration, and frequency of use of the diagnostic radiopharmaceutical; the half-life of the ligand, carrier, and radionuclide; and results of clinical studies. In the medical imaging guidance, FDA will establish categories of diagnostic radiopharmaceuticals based on defined characteristics relevant to safety risk and will specify the amount and type of safety data that is appropriate for each category (e.g., required safety data may be limited for diagnostic radiopharmaceuticals with a well established, low-risk profile). Based on its review of the previously listed product characteristics and safety information, FDA will place each diagnostic radiopharmaceutical into the appropriate safety risk category.

28. One comment stated that the regulation should specify a procedure by which a sponsor may provide FDA with information on the basis of which the agency can categorize a diagnostic radiopharmaceutical according to new safety data required. The comment maintained that this would enable manufacturers to make product development decisions with the assurance that a categorization process will be available and applied consistently. The comment recommended that the categorization procedure provide for the following: (1) Sponsor submission of a request for low-risk designation at a meeting prior to the submission of an investigational new drug application (IND) or any subsequent time; (2) FDA designation of the product as low risk if the sponsor submits preclinical data, clinical data, and/or other information demonstrating that the radiopharmaceutical possesses the characteristics of a low-risk category drug; and (3) FDA action on a designation request within 30 days of submission.

FDA agrees that there should be a standard procedure that the sponsor of a diagnostic radiopharmaceutical may follow to request that the agency assign the radiopharmaceutical to a particular safety risk category. FDA also agrees that such procedure should specify, among other things, when a request for categorization may be made and the information that should be submitted with a request. However, FDA believes that it is more practical to address this matter in the medical imaging guidance rather than in regulations.

29. One comment requested that proposed §§ 315.6(c)(2) and 601.35(c)(2) be revised to clarify that a diagnostic radiopharmaceutical that has not been previously approved may be eligible for low-risk categorization. The comment noted that this would allow low-risk categorization of a previously unapproved radiopharmaceutical when (1) there is a history of safe use of the radiopharmaceutical's ligand or carrier or (2) the sponsor submits sufficient preclinical and toxicology data on the radiopharmaceutical itself.

FDA agrees that, under §§ 315.6(c)(2) and 601.35(c)(2), a diagnostic radiopharmaceutical that has not been previously approved may be eligible for placement in a low-risk category under certain circumstances, such as those suggested by the comment. However, FDA finds it unnecessary to revise these sections of the regulations to specifically refer to diagnostic radiopharmaceuticals that have not been previously approved because the rule does not address the approval status of the radiopharmaceuticals. The agency intends to revise the medical imaging draft guidance to clarify that even a diagnostic radiopharmaceutical that has

not been previously approved may, under certain circumstances, fall within a low-risk category.

30. Proposed §§ 315.6(d) and 601.35(d) stated that a radiation safety assessment would establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. In making such an evaluation, dosimetry to the total body, to specific organs or tissues, and, if appropriate, to target organs or tissues must be considered, although the maximum tolerated dose need not be established.

One comment stated that a radiation safety assessment should usually consist of an estimate of radiation absorbed dose in a few normal subjects and that there is no need for subjects with renal or hepatic insufficiency or other diseases. The comment maintained that precise dosimetry is usually unnecessary, especially for Tc–99m agents, because absorbed doses are insignificant. The comment added that even though some radionuclides may give selected organ doses that are not insignificant, such doses are low and have not been associated with any hazard.

FDA does not agree that it is unnecessary to measure dosimetry and to assess the radiation safety of a diagnostic radiopharmaceutical. FDA agrees that current knowledge suggests that absorbed radiation doses from some diagnostic radiopharmaceuticals are not significant. However, as the comment notes, the experience with dosimetry and radiation safety demonstrates that this is not true for all diagnostic radiopharmaceuticals. Because the agency does not know the future significance of the absorbed radiation dose of a particular diagnostic radiopharmaceutical, current standardized dosimetry measurements are needed for all diagnostic radiopharmaceuticals. These standardized dosimetry measurements ensure that the absorbed radiation dose of a particular diagnostic radiopharmaceutical is recorded in a standardized procedure and that the current known risk of radiation injury from the radiopharmaceutical is as low as possible.

31. There were three comments on evaluation of radiation dosimetry. Two comments objected to the use of dosimetry to the total body because it assumes uniform, homogenous distribution of a radiopharmaceutical throughout the body. The comments contended that this is inaccurate because diagnostic radiopharmaceuticals must localize in certain organs or tissues to be clinically useful and because essentially all diagnostic radiopharmaceuticals undergo some type of elimination from the body that leads to concentration in the kidneys/urinary tract or liver/biliary tract/gastrointestinal tract. The comments maintained that because diagnostic radiopharmaceuticals are heterogeneously concentrated in various organs and tissues having different radiosensitivities, the radiation safety assessment should consider radiation absorbed doses for all organs and tissues in conjunction with their relative radiosensitivities using a so-called ''effective dose'' calculation.

FDA acknowledges that a diagnostic radiopharmaceutical is not distributed uniformly throughout the body but rather localizes in particular organs or tissues. Although FDA agrees that effective dose is a relevant measure of dosimetry, the measurement of total body dosimetry also may provide relevant information in some settings. FDA believes that each sponsor should use dosimetry measurements that are appropriate for a particular diagnostic radiopharmaceutical in the defined clinical setting, whether this requires measurement of dosimetry to the total body, to specific organs or tissues, and/or to target organs or tissues. However, FDA concludes that it is more appropriate to address this matter in the medical imaging guidance rather than the regulations so that dosimetry evaluations of diagnostic radiopharmaceuticals may better reflect developments in radiopharmaceutical science. Consequently, the agency is deleting the sentence in proposed §§ 315.6(d) and 601.35(d) specifying what must be considered in a radiation dosimetry evaluation.

32. A third comment on evaluation of radiation dosimetry noted that the ''Guideline for the Clinical Evaluation of Radiopharmaceutical Drugs'' states that organ and tissue dosimetries are required only in preclinical studies; for clinical studies, dosimetry calculations should be made only on the primary organ(s) of interest and should follow the system specified by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine. The comment recommended that the final rule include similar recommendations. The comment also maintained that the final rule must distinguish preclinical from clinical expectations.

FDA believes that the appropriate design of the preclinical and clinical dosimetry studies for determining radiation dosimetry must be based on the characteristics of the radiopharmaceutical, e.g., biodistribution, pharmacological actions, and clearance pathways. FDA intends to address in the medical imaging guidance the preclinical and clinical dosimetry measurements that are considered currently appropriate for different types of diagnostic radiopharmaceuticals. Therefore, FDA declines to include in the regulations specific methods or models of dosimetry or to distinguish between the preclinical and clinical dosimetry requirements in the regulations.

33. There were two comments on maximum tolerated dose. One comment found the statement that the maximum tolerated dose need not be established to be ''curious'' because the maximum tolerated radiation dose was established decades ago. One comment asked that FDA clarify whether the phrase refers to the maximum tolerated dose associated with adverse events and laboratory abnormalities or to the maximum tolerated dose based on radiation dosimetry.

By stating in §§ 315.6(d) and 601.35(d) that the maximum tolerated dose need not be established, FDA is simply clarifying that there is no need to determine the maximum tolerated dose of radiation as part of the radiation dosimetry evaluation.

IV. Analysis of Economic Impacts

FDA has examined the impact of the final rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze significant regulatory options that would minimize any significant economic impact of a rule on small entities. The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any mandate that results in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any 1 year.

The agency has reviewed this final rule and has determined that it is consistent with the principles set forth in the Executive Order and in these two statutes. FDA finds that, while the rule

will not be an economically significant rule, it is a significant regulatory action as described in section 3 paragraph (f)(4) of the Executive Order. Further, the agency finds that, under the Regulatory Flexibility Act, the rule will not have a significant economic impact on a substantial number of small entities. Also, since the expenditures resulting from the standards identified in the rule are less than $100 million, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

The final rule clarifies existing FDA requirements for the approval and evaluation of drug and biological products already in place under the act and the PHS Act. Existing regulations (parts 314 and 601) specify the type of information that manufacturers are required to submit so that the agency may properly evaluate the safety and effectiveness of new drugs or biological products. Such information is usually submitted as part of an NDA, BLA, or supplement to an approved application. The information typically includes both nonclinical and clinical data concerning the product's pharmacology, toxicology, adverse events, radiation safety assessments, chemistry, and manufacturing and controls. The final regulation recognizes the unique characteristics of diagnostic radiopharmaceuticals and sets out the agency's approach to the evaluation of these products. For certain diagnostic radiopharmaceuticals, the final regulation may reduce the amount of safety information that an applicant must obtain by conducting new clinical studies. This would include approved radiopharmaceuticals with well established, low-risk safety profiles because such products might be able to use scientifically sound data established during use of the radiopharmaceutical to support the approval of a new indication for use. In addition, the clarification achieved by the final rule is expected to reduce the costs of submitting an application for approval of a diagnostic radiopharmaceutical by improving communications between applicants and the agency and by reducing wasted effort directed toward the submission of data that is not necessary to meet the statutory approval standard.

Manufacturers of diagnostic radiopharmaceuticals are defined by the Small Business Administration as small businesses if such manufacturers employ fewer than 500 employees. The agency finds that only 2 of the 8 companies that currently manufacture or market radiopharmaceuticals have fewer than 500 employees.[1] Moreover, the final rule would not impose any additional costs but, rather, might reduce the clinical costs associated with the existing regulations by clarifying data submission requirements. One comment stated that the regulatory costs currently associated with developing new radiopharmaceuticals have made it difficult for more than two small entities to stay in business. While the agency is not aware of any safe and effective radiopharmaceuticals that have been prevented from entering the marketplace, it believes that this rule might reduce costs and therefore benefit small entities. Therefore, in accordance with the Regulatory Flexibility Act, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

V. The 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 (PRA) (44 U.S.C. 3501–3520). The title, description, and the 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 the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring.

Description: FDA is finalizing regulations for the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring. The final rule clarifies existing FDA requirements for approval and evaluation of drug and biological products already in place under the authorities of the act and the PHS Act. Those regulations, which appear primarily in parts 314 and 601, specify the information that manufacturers must submit to FDA for the agency to properly evaluate the safety and effectiveness of new drugs or biological products. The information, which is usually submitted as part of an NDA or BLA, or as a supplement to an approved application, typically includes, but is not limited to, nonclinical and clinical data on the pharmacology, toxicology, adverse events, radiation safety assessments, and chemistry, manufacturing, and controls. The content and format of an application for approval of a new drug are set out in § 314.50 and for a new biological product in § 601.2. Under part 315 and §§ 601.30 through 601.35 of part 601, information required under the act and the PHS Act, and needed by FDA to evaluate the safety and effectiveness of in vivo radiopharmaceuticals, will still need to be reported.

Description of Respondents: Manufacturers of in vivo radiopharmaceuticals used for diagnosis and monitoring.

As required by section 3506 (c)(2)(B) of the PRA, FDA provided an opportunity for public comment on May 22, 1998 (63 FR 28301), on the information collection provisions of the proposed rule. FDA received one comment on the information collection provisions. The comment stated that use of the figure of seven approved diagnostic radiopharmaceuticals in fiscal year 1997 (FY 1997) resulted in a very low estimate of the expected number of future annual applications. The comment suggested that 50 applications would be a more appropriate figure.

Based on 5 years of experience, FDA believes that the estimate of the number of applications for approval of in vivo diagnostic radiopharmaceuticals is a reasonable one. In FY 1992 to 1997, FDA approved 13 in vivo diagnostic radiopharmaceuticals. In FY 1998, only one such product was approved. The agency does not expect an increase in applications for approval of diagnostic radiopharmaceuticals in the near future. Although sponsors may submit higher numbers of IND's for diagnostic radiopharmaceuticals each year, the annual number of NDA's, abbreviated new drug applications, and BLA's approved is small. FDA therefore declines to change its estimate.

In a notice of action on the proposed rule dated July 17, 1998, OMB stated that it had concerns about the utility and burden of the information collected to demonstrate the safety and effectiveness of a new diagnostic radiopharmaceutical or of a new indication for use of an approved diagnostic radiopharmaceutical. OMB maintained that the burden and utility of this information collection should be assessed in light of public comments on the proposed rule and that FDA should specifically address such comments in the preamble to the final rule.

Section 122 of the Modernization Act directs FDA to develop regulations on the approval of diagnostic radiopharmaceuticals under section 505 of the act. As discussed previously, FDA

[1] *Medical & Healthcare Marketplace Guide*, 13th ed., Dorland's Directories, 1997.

received only one comment on the information collection provisions of the proposed rule. None of the manufacturers of diagnostic radiopharmaceuticals who submitted comments on the proposed rule questioned the need for the submission of information to demonstrate the safety and effectiveness of a product to obtain marketing approval. Rather, their comments primarily sought clarification or proposed minor modification of the proposed regulations.

To estimate the potential number of respondents that would submit applications or supplements for diagnostic radiopharmaceuticals, FDA used the number of approvals granted in FY 1997 to approximate the number of future annual applications. In FY 1997, FDA approved seven diagnostic radiopharmaceuticals and received one new indication supplement; of these, three respondents received approval through the Center for Drug Evaluation and Research and five received approval through the Center for Biologics Evaluation and Research. The annual frequency of responses was estimated to be one response per application or supplement. The hours per response refers to the estimated number of hours that an applicant would spend preparing the information required by the final regulations. Based on FDA's experience, the agency estimates the time needed to prepare a complete application for a diagnostic radiopharmaceutical to be approximately 10,000 hours, roughly one-fifth of which, or 2,000 hours, is estimated to be spent preparing the portions of the application that are affected by these final regulations. The final rule would not impose any additional reporting burden for safety and effectiveness information on diagnostic radiopharmaceuticals beyond the estimated current burden of 2,000 hours because safety and effectiveness information is already required by § 314.50 under OMB control number 0910–0001 and § 601.2 under OMB control number 0910–0124. In fact, clarification in the final rule of FDA's standards for evaluation of diagnostic radiopharmaceuticals is expected to streamline overall information collection burdens, particularly for diagnostic radiopharmaceuticals that may have well established, low-risk safety profiles, by enabling manufacturers to tailor information submissions and avoid conducting unnecessary clinical studies. The following table indicates estimates of the annual reporting burdens for the preparation of the safety and effectiveness sections of an application that are imposed by existing regulations, §§ 314.50 and 601.2. The burden totals do not include an increase in burden because no increase is anticipated. This estimate does not include the actual time needed to conduct studies and trials or other research from which the reported information is obtained.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
315.4, 315.5, and 315.6	3	1	3	2,000	6,000
601.33, 601.34, and 601.35	5	1	5	2,000	10,000
Total	8		8		16,000

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

The information collection provisions of the final rule have been submitted to OMB for review. Prior to the effective date of the 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 the 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.

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.

List of Subjects

21 CFR Part 315

Biologics, Diagnostic radiopharmaceuticals, Drugs.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, the Food and Drug Administration Modernization Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter I is amended to read as follows:

1. Part 315 is added to read as follows:

PART 315—DIAGNOSTIC RADIOPHARMACEUTICALS

Sec.
315.1 Scope.
315.2 Definition.
315.3 General factors relevant to safety and effectiveness.
315.4 Indications.
315.5 Evaluation of effectiveness.
315.6 Evaluation of safety.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 315.1 Scope.

The regulations in this part apply to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. They do not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical must be evaluated taking into account each intended use.

§ 315.2 Definition.

For purposes of this part, *diagnostic radiopharmaceutical* means:

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§ 315.3 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical includes consideration of the following:

(a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine,

(b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical), and

(c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§ 315.4 Indications.

(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:

(1) Structure delineation;

(2) Functional, physiological, or biochemical assessment;

(3) Disease or pathology detection or assessment; and

(4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

§ 315.5 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation varies depending upon the proposed indication(s) and may use one or more of the following criteria:

(1) The claim of structure delineation is established by demonstrating in a defined clinical setting the ability to locate anatomical structures and to characterize their anatomy.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of function(s) or physiological, biochemical, or molecular process(es).

(3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.

(4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in § 315.4, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

(b) The accuracy and usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status must be established in another manner, e.g., patient followup.

§ 315.6 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following:

(1) The radiation dose;

(2) The pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand;

(3) The risks of an incorrect diagnostic determination;

(4) The adverse reaction profile of the drug;

(5) Results of human experience with the radiopharmaceutical for other uses; and

(6) Results of any previous human experience with the carrier or ligand of the radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

(1) Allergic or hypersensitivity responses,

(2) Immunologic responses,

(3) Changes in the physiologic or biochemical function of the target and nontarget tissues, and

(4) Clinically detectable signs or symptoms.

(c)(1) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:

(i) Pharmacology data,

(ii) Toxicology data,

(iii) Clinical adverse event data, and

(iv) Radiation safety assessment.

(2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical, and its carrier or ligand, obtained from other studies and uses. Such information may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies. FDA will establish categories of diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data that are appropriate for each category (e.g., required safety data may be limited for diagnostic radiopharmaceuticals with a well established, low-risk profile). Upon reviewing the relevant product characteristics and safety information, FDA will place each diagnostic radiopharmaceutical into the appropriate safety risk category.

(d) Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. The maximum tolerated dose need not be established.

PART 601—LICENSING

2. The authority citation for part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.33 [Redesignated as § 601.28]

3. Section 601.33 is redesignated as § 601.28 and transferred from subpart D to subpart C, and the redesignated section heading is revised to read as follows:

§ 601.28 Foreign establishments and products: samples for each importation.

* * * * *

4. Subpart D is revised to read as follows:

Subpart D—Diagnostic Radiopharmaceuticals

Sec.

601.30 Scope.
601.31 Definition.
601.32 General factors relevant to safety and effectiveness.
601.33 Indications.
601.34 Evaluation of effectiveness.
601.35 Evaluation of safety.

Subpart D—Diagnostic Radiopharmaceuticals

§ 601.30 Scope.

This subpart applies to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. It does not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical must be evaluated taking into account each intended use.

§ 601.31 Definition.

For purposes of this part, *diagnostic radiopharmaceutical* means:

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§ 601.32 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical includes consideration of the following:

(a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;

(b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and

(c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§ 601.33 Indications.

(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:

(1) Structure delineation;

(2) Functional, physiological, or biochemical assessment;

(3) Disease or pathology detection or assessment; and

(4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

§ 601.34 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation varies depending upon the proposed indication(s) and may use one or more of the following criteria:

(1) The claim of structure delineation is established by demonstrating in a defined clinical setting the ability to locate anatomical structures and to characterize their anatomy.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of function(s) or physiological, biochemical, or molecular process(es).

(3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.

(4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in § 601.33, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

(b) The accuracy and usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status must be established in another manner, e.g., patient followup.

§ 601.35 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following:

(1) The radiation dose;

(2) The pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand;

(3) The risks of an incorrect diagnostic determination;

(4) The adverse reaction profile of the drug;

(5) Results of human experience with the radiopharmaceutical for other uses; and

(6) Results of any previous human experience with the carrier or ligand of the radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

(1) Allergic or hypersensitivity responses,

(2) Immunologic responses,

(3) Changes in the physiologic or biochemical function of the target and nontarget tissues, and

(4) Clinically detectable signs or symptoms.

(c)(1) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:

(A) Pharmacology data,

(B) Toxicology data,

(C) Clinical adverse event data, and

(D) Radiation safety assessment.

(2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical, and its carrier or ligand, obtained from other studies and uses. Such information may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies. FDA will establish categories of diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data that are appropriate for each category (e.g., required safety data may be limited for diagnostic radiopharmaceuticals with a well established, low-risk profile). Upon reviewing the relevant product characteristics and safety information, FDA will place each diagnostic radiopharmaceutical into the appropriate safety risk category.

(d) Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. The maximum tolerated dose need not be established.

Dated: April 16, 1999.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 99–12320 Filed 5–14–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 522

Implantation or Injectable Dosage Form New Animal Drugs; Oxytetracycline Injection

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental abbreviated new animal drug application (ANADA) filed by Boehringer Ingelheim Vetmedica, Inc. The supplemental ANADA provides for establishment of a 28-day withdrawal period for subcutaneous use of oxytetracycline injection in cattle and for intramuscular use in swine.

EFFECTIVE DATE: May 17, 1999.

FOR FURTHER INFORMATION CONTACT: William T. Flynn, Center for Veterinary Medicine (HFV–133), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–7570.

SUPPLEMENTARY INFORMATION: Boehringer Ingelheim Vetmedica, Inc., 2621 North Belt Highway, St. Joseph, MO 64506, filed supplemental ANADA 200–008 that provides for establishment of a 28-day withdrawal period for subcutaneous use in cattle and intramuscular use in swine of Oxytet™ 200 and Bio-Mycin® 200 (oxytetracycline injection). The 28-day withdrawal period for the intravenous and intramuscular use of oxytetracycline injection in cattle, assigned as part of the original approval, remains unchanged. The drug is for intramuscular, subcutaneous, or intravenous treatment of beef cattle and nonlactating dairy cattle as follows: (1) Bacterial pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; (2) infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*; (3) foot rot and diptheria caused by *Fusobacterium necrophorum*; (4) bacterial enteritis (scours) caused by *Escherichia coli*; (5) wooden tongue caused by *Actinobacillus lignieresii*; (6) leptospirosis caused by *Leptospira pomona*; and (7) wound infections and acute metritis caused by strains of streptococcal and staphylococcal organisms. The drug is for intramuscular use in swine for treatment of bacterial enteritis (scours, colibacillosis) caused by *E. coli*, pneumonia caused by *P. multocida*, and leptospirosis caused by *L. pomona*, and in sows as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *E. coli*. The ANADA is approved as of March 16, 1999, and the regulations are amended by revising § 522.1660(d)(2)(iii) (21 CFR 522.1660(d)(2)(iii)) to reflect the approval. Because the current regulation failed to reflect the previously established 36-day withdrawal period for subcutaneous use of oxytetracycline injection in cattle, no revision to § 522.1660(d)(1)(iii) is required for this supplemental approval that establishes a 28-day withdrawal period for subcutaneous use of oxytetracycline injection in cattle. The basis of approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.33(a)(1) 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.

List of Subjects in 21 CFR Part 522

Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 522 is amended as follows:

PART 522—IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 522 continues to read as follows:

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

2. Section 522.1660 is amended by revising paragraph (d)(2)(iii) to read as follows:

§ 522.1660 Oxytetracycline injection.

* * * * *

(d) * * *

(2) * * *

(iii) *Limitations.* Administer intramuscularly. Do not inject more than 5 milliliters per site in adult swine. Discontinue treatment at least 28 days prior to slaughter when provided by 000010, 000069, 011722, 053389, 059130, and 061623.

Dated: May 3, 1999.

Margaret Ann Miller,

Acting Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 99–12284 Filed 5–14–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 522 and 556

Implantation or Injectable Dosage Form New Animal Drugs; Ivermectin; Ivermectin and Clorsulon

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of two supplemental new animal drug applications (NADA's) filed by Merial Ltd. One supplement provides for use of ivermectin injection, and the other provides for the use of ivermectin and clorsulon injection, for 28-day persistent control of lungworms in cattle. In addition, a tolerance for ivermectin residues in cattle muscle is established.

EFFECTIVE DATE: May 17, 1999.

FOR FURTHER INFORMATION CONTACT: Janis R. Messenheimer, Center for Veterinary Medicine (HFV–135), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–7578.

SUPPLEMENTARY INFORMATION: Merial Ltd., 2100 Ronson Rd., Iselin, NJ 08830–3077, is sponsor of NADA 128–409 that provides for use of Ivomec® Injection (1 percent ivermectin) and NADA 140–833 that provides for use of Ivomec® Plus Injection (1 percent ivermectin and 10 percent clorsulon) in cattle. The NADA's provide for use of the drugs for the treatment and control of gastrointestinal roundworm, lungworm,