whichever occurs later, and thereafter at intervals not to exceed 3,000 landings, inspect the wing front attachments (both the wing sides and fuselage sides) in accordance with Socata Service Bulletin No. SB 10–081–57, Amendment 1, dated August 1996.

(b) For all affected airplanes, accomplish the following on the wing front attachments on the wing sides:

(1) If no cracks are found on the wing front attachments on the wing sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 6,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 911000 in accordance with Socata Technical Instruction No. 9110, which incorporates the following pages:

Pages	Revision level	Date
0 and 1	Amendment	January 31, 1992.
2 through 11	Original Issue	October 1985.

(2) If a crack(s) is found on the wing front attachments on the wing sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 911000 in accordance with Socata Technical Instruction No. 9110. Incorporate this kit at intervals not to exceed 6,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(c) For Models TB9 and TB10 airplanes, with a serial number in the range of 1 through 399, or with a serial number of 413; that do not have either Socata Service Letter (SL) 10–14 incorporated or Socata Modification Kit OPT10 908100 incorporated, accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 6,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198–53, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198–53, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(d) For Models TB9 and TB10 airplanes, with a serial number in the range of 1 through 399, or with a serial number of 413; that have either Socata Service Letter (SL) 10–14 incorporated or Socata Modification Kit OPT10 908100 incorporated, accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198–53, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198–53, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(e) For Models TB9 and TB10 airplanes, with a serial number in the range of 400 through 412, or with a serial number in the range of 414 through 9999; accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 908100 in accordance with Socata Technical Instruction of Modification OPT10 9181–53, Amendment 2, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 908100 in accordance with Socata Technical Instruction of Modification OPT10 9181–53, Amendment 2, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

Note 3: ''Unless already accomplished'' credit may be used if the kits that are required by paragraphs (c)(1), (d)(1), and (e)(1) of this AD are aleady incorporated on the applicable airplanes. As specified in the AD, repetitive incorporation of these kits would still be required at intervals not to exceed 12,000 landings provided no cracks are found.

(f) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

(g) An alternative method of compliance or adjustment of the initial or repetitive compliance times that provides an equivalent level of safety may be approved by the Manager, Small Airplane Directorate, FAA, 1201 Walnut, suite 900, Kansas City, Missouri 64106. The request shall be forwarded through an appropriate FAA Maintenance Inspector, who may add comments and then send it to the Manager, Small Airplane Directorate.

Note 4: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Small Airplane Directorate.

(h) Questions or technical information related to the service information referenced in this AD should be directed to the SOCATA—Groupe AEROSPATIALE, Socata Product Support, Aeroport Tarbes-Ossun-Lourdes, B P 930, 65009 Tarbes Cedex, France; telephone: 33–5–62–41–76–52; facsimile: 33–5–62–41–76–54; or the Product Support Manager, SOCATA Aircraft, North Perry Airport, 7501 Pembroke Road, Pembroke Pines, Florida 33023; telephone: (954) 893–1400; facsimile: (954) 964–1402. This service information may be examined at the FAA, Central Region, Office of the Regional Counsel, Room 1558, 601 E. 12th Street, Kansas City, Missouri.

Note 5: The subject of this AD is addressed in French AD 94–264(A), dated December 7, 1994.

Issued in Kansas City, Missouri, on May 14, 1998.

Michael Gallagher,

Manager, Small Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98–13653 Filed 5–21–98; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 315 and 601

[Docket No. 98N–0040]

Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA), in response to the requirements of the Food and Drug Administration Modernization Act of 1997 (FDAMA), is proposing to amend the drug and biologics regulations by adding provisions that would clarify the evaluation and approval of in vivo

radiopharmaceuticals used in the diagnosis or monitoring of diseases. The proposed regulations would describe certain types of indications for which FDA may approve diagnostic radiopharmaceuticals. The proposed rule also would include criteria that the agency would use to evaluate the safety and effectiveness of a diagnostic radiopharmaceutical under the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act (the PHS Act).

DATES: Submit comments on this proposed rule on or before August 5, 1998. Submit written comments on the information collection provisions by June 22, 1998. See section IV of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit comments of the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Dano B. Murphy, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210; or Brian L. Pendleton, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5649.

SUPPLEMENTARY INFORMATION:

I. Introduction

Radiopharmaceuticals are used for a wide variety of diagnostic, monitoring, and therapeutic purposes. Diagnostic radiopharmaceuticals are used to image or otherwise identify an internal structure or disease process, while therapeutic radiopharmaceuticals are used to effect a change upon a targeted structure or disease process.

The action of most radiopharmaceuticals is derived from two components: A nonradioactive delivery component, i.e., a carrier and/or ligand; and a radioactive imaging component, i.e., a radionuclide. Nonradioactive delivery ligands and carriers are usually peptides, small proteins, or antibodies. The purpose of ligands and carriers is to direct the radionuclide to a specific body location or process. Once a radiopharmaceutical has reached its targeted location, the radionuclide component can be detected. The imaging component usually is a short-lived radioactive molecule that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. The emitted photons are detected by specialized devices that generate images of, or otherwise detect, radioactivity, such as nuclear medicine cameras and radiation detection probe devices.

On November 21, 1997, the President signed FDAMA into law. Section 122(a)(1) of FDAMA directs FDA to issue proposed and final regulations on the approval of diagnostic radiopharmaceuticals within specific timeframes. As defined in section 122(b) of FDAMA, a radiopharmaceutical is an article ''that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans * * * that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons[,] or * * * any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article.'' Section 122(a)(1)(A) of FDAMA states that FDA regulations will provide that, in determining the safety and effectiveness of a radiopharmaceutical under section 505 of the act (for a drug) (21 U.S.C. 355) or section 351 of the PHS Act (for a biological product) (42 U.S.C. 262), the agency will consider the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component), and the estimated absorbed radiation dose of the radiopharmaceutical.

FDAMA requires FDA to consult with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry before proposing any regulations governing the approval of radiopharmaceuticals. Accordingly, in the **Federal Register** of February 2, 1998 (63 FR 5338), FDA published a notification of a public meeting entitled ''Developing Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring.'' The notice invited all interested persons to attend the meeting, scheduled for February 27, 1998, and to comment on how the agency should regulate radiopharmaceuticals. In particular, FDA invited comment on the following topics: (1) The effect of the use of a radiopharmaceutical in the practice of medicine on the nature and extent of safety and effectiveness evaluations; (2) the general characteristics of a radiopharmaceutical that should be considered in the preclinical and clinical pharmacological and toxicological evaluations of a radiopharmaceutical (including the radionuclide as well as the ligand and carrier components); (3) determination and consideration of a radiopharmaceutical's estimated absorbed radiation dose in humans; and (4) the circumstances under which an approved indication for marketing might refer to manifestations of disease (biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.

Approximately 50 individuals from industry, academic institutions, professional medical organizations, and patient advocacy groups attended the February 27, 1998, public meeting and/or submitted comments in response to the notice. FDA has considered all of these comments in drafting this proposed rule.

The proposed rule applies to the approval of in vivo radiopharmaceuticals (both drugs and biologics) used for diagnosis and monitoring. The proposed regulations will not apply to radiopharmaceuticals used for therapeutic purposes. The regulations include a definition of diagnostic radiopharmaceuticals (which includes radiopharmaceuticals used for monitoring) and provisions that address the following aspects of diagnostic radiopharmaceuticals: (1) General factors to be considered in determining safety and effectiveness, (2) possible indications for use, (3) evaluation of effectiveness, and (4) evaluation of safety.

To establish these regulations, FDA proposes to add a new part 315 to title 21 of the Code of Federal Regulations (CFR) and to rename subpart D and add §§ 601.30 through 601.35 in part 601 (21 CFR part 601). These new provisions would complement and clarify existing regulations on the approval of drugs and biologics in parts 314 (21 CFR parts 314) and 601, respectively. In addition to these regulatory changes, FDA is 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. This guidance will address the application of the proposed rule. FDA will make such guidance available in draft form for public comment in accordance with the agency's Good Guidance Practices (see 62 FR 8961, February 27, 1997).

Positron emission tomography (PET) drugs are a particular type of radiopharmaceutical. Section 121 of FDAMA addresses these products

separately from other diagnostic radiopharmaceuticals and requires FDA to develop appropriate approval procedures and current good manufacturing practice requirements for PET products within the next 2 years. Although FDA expects the standards for determining the safety and effectiveness of diagnostic radiopharmaceuticals set forth in this proposed rule to apply to PET diagnostic products under the approval procedures that FDA intends to develop for those products, the agency will address this issue when it publishes its proposal on PET drugs.

II. Description of the Proposed Rule

The proposed rule would add a new part 315 to the CFR containing provisions on radiopharmaceutical drugs subject to section 505 of the act that are used for diagnosis and monitoring. Corresponding provisions applicable to radiopharmaceutical biological products subject to licensure under section 351 of the PHS Act would be set forth in revised subpart D of part 601. Both proposed regulations are discussed in the following section of this document.

A. Scope

Proposed §§ 315.1 and 601.30 define the scope of the diagnostic radiopharmaceutical provisions, i.e., that they apply only to radiopharmaceuticals used for diagnosis and monitoring and not to radiopharmaceuticals intended for therapeutic uses. FDA intends that these regulations will apply only to diagnostic radiopharmaceuticals that are administered in vivo. In vitro diagnostic products generally are regulated as medical devices under the act, although they may also be biological products subject to licensure under section 351 of the PHS Act (see 21 CFR 809.3(a)).

Some radiopharmaceuticals may have utility as both diagnostic and therapeutic drugs or biologics. When a particular radiopharmaceutical drug or biologic is proposed for both diagnostic and therapeutic uses, FDA will evaluate the diagnostic claims under the provisions in part 315 (for drugs) or subpart D of part 601 (for biologics) and evaluate the therapeutic claims under the regulations applicable to other drug or biologic applications.

B. Definition

The proposed ruling in §§ 315.2 and 601.31 would include a definition of ''diagnostic radiopharmaceutical'' that is identical to the definition of ''radiopharmaceutical'' in section 122(b) of FDAMA. Thus, a ''diagnostic radiopharmaceutical'' would be defined as 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 any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article. FDA interprets ''disease or a manifestation of a disease'' to include conditions that may not ordinarily be considered diseases, such as essential thrombocytopenia and bone fractures. In addition, FDA interprets the definition as including articles that exhibit spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons.

C. General Factors Relevant to Safety and Effectiveness

In §§ 315.3 and 601.32, FDA proposes to incorporate in its regulations the requirement in section 122 of FDAMA that the agency consider certain factors in determining the safety and effectiveness of diagnostic radiopharmaceuticals under section 505 of the act or section 351 of the PHS Act. These factors are as follows: (1) The proposed use of a diagnostic radiopharmaceutical in the practice of medicine; (2) the pharmacological and toxicological activity of a diagnostic radiopharmaceutical, including any carrier or ligand component; and (3) the estimated absorbed radiation dose of the diagnostic radiopharmaceutical. Other sections of the proposed regulations describe how the agency will assess these factors. In addition, FDA intends to provide further information in guidance to industry.

D. Indications

In §§ 315.4(a) and 601.33(a), FDA proposes to specify some of the types of indications for which the agency may approve a diagnostic radiopharmaceutical. These categories of indications are as follows: (1) Structure delineation; (2) functional, physiological, or biochemical assessment; (3) disease or pathology detection or assessment; and (4) diagnostic or therapeutic management. Approval may be possible for claims other than those listed. (In these and other provisions on diagnostic radiopharmaceuticals in the proposed rule, the terms ''indication,'' ''indication for use,'' and ''claim'' have the same meaning and are used interchangeably.)

A diagnostic radiopharmaceutical that is intended to provide structural delineation is designed to locate and outline anatomic structures. For example, a radiopharmaceutical might be developed to distinguish a structure that cannot routinely be seen by any other imaging modality, such as a drug designed to image the lymphatics of the small bowel.

A diagnostic radiopharmaceutical that is intended to provide a functional, physiological, or biochemical assessment is used to evaluate the function, physiology, or biochemistry of a tissue, organ system, or body region. Functional, physiological, and biochemical assessments are designed to determine if a measured parameter is normal or abnormal. Examples of a functional or physiological assessment include the determination of the cardiac ejection fraction, myocardial wall motion, and cerebral blood flow. Examples of a biochemical assessment include the evaluation of sugar, lipid, protein, or nucleic acid synthesis or metabolism.

A diagnostic radiopharmaceutical that is intended to provide disease or pathology detection or assessment information assists in the detection, location, or characterization of a specific disease or pathological state. Examples of this type of diagnostic radiopharmaceutical include a radiolabeled monoclonal antibody used to attach to a specific tumor antigen and thus detect a tumor and a peptide that participates in an identifiable transporter function associated with a specific neurological disease.

A diagnostic radiopharmaceutical that is intended to assist in diagnostic or therapeutic patient management provides imaging, or related, information leading directly to a diagnostic or therapeutic patient management decision. Examples of this type of indication include: (1) Assisting in a determination of whether a patient should undergo a diagnostic coronary angiography or will have predictable clinical benefit from a coronary revascularization, and (2) assisting in a determination of the resectability of a primary tumor.

Proposed §§ 315.4(b) and 601.33(b) reflect the intent of section 122(a)(2) of FDAMA, which states that in appropriate cases, FDA may approve a diagnostic radiopharmaceutical for an indication that refers to ''manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.'' Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a process or to more than one disease or condition. This would allow FDA to approve a product

for an indication (e.g., delineation of a particular anatomic structure or functional assessment of a specific organ system) that would encompass manifestations of disease that are common to multiple disease states. An example of a manifestation that is common to multiple diseases is tumor metastases to the liver caused by various malignancies.

E. Evaluation of Effectiveness

The specific criteria that FDA would use to evaluate the effectiveness of a diagnostic radiopharmaceutical are stated in proposed §§ 315.5(a) and 601.34(a). These provisions state that FDA assesses the effectiveness of a diagnostic radiopharmaceutical by evaluating its ability to provide useful clinical information that is related to its proposed indication for use. The nature of the indication determines the method of evaluation, and because an application may include more than one type of claim, FDA might need to employ multiple evaluation criteria. FDA would require that any such claim be supported with information demonstrating that the potential benefit of the diagnostic radiopharmaceutical outweighs the risk to the patient from administration of the product.

Under proposed §§ 315.5(a)(1) and 601.34(a)(1), a claim of structure delineation would be established by demonstrating the ability of a diagnostic radiopharmaceutical to locate and characterize normal anatomic structures. In §§ 315.5(a)(2) and 601.34(a)(2), FDA proposes that a claim of functional, physiological, or biochemical assessment would be established by demonstrating that the diagnostic radiopharmaceutical could reliably measure the function or the physiological, biochemical, or molecular process. A reliable measurement would need to be supported by studies in normal and abnormal patient populations, consistent with the proposed claim and would require a qualitative or quantitative understanding of how the measurement varies in normal and abnormal subjects.

The agency proposes, in §§ 315.5(a)(3) and 601.34(a)(3), that a claim of disease or pathology detection or assessment would be established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical had sufficient accuracy in identifying or characterizing the disease or pathology. The term ''accuracy'' refers to the diagnostic performance of the product as measured by factors such as sensitivity, specificity, positive predictive value, negative predictive value, and reproducibility of test interpretation. The term ''sufficient accuracy'' means accuracy that is good enough to indicate that the product would be useful in one or more clinical settings. FDA believes that the data demonstrating accuracy must be obtained from patients in a clinical setting(s) reflecting the proposed indication(s). For example, if a claim is for diagnosis of tumor in patients with a negative computed tomography (CT) scan for disease and a borderline serum carcinoembryonic antigen (CEA), the accuracy of the diagnostic radiopharmaceutical should be assessed in such patients rather than only in patients with CT-diagnosed disease or high serum CEA.

Under proposed §§ 315.5(a)(4) and 601.34(a)(4), for a claim of diagnostic or therapeutic patient management, the applicant must establish effectiveness by demonstrating in a defined clinical setting that the test is useful in such patient management. For example, an imaging agent might be studied in a manner that would demonstrate its usefulness in directing local excision of cancer-laden lymph nodes and sparing a wide area of nondiseased lymphatic tissue.

In §§ 315.5(a)(5) and 601.34(a)(5), FDA proposes that, for claims that do not fall within the indication categories in §§ 315.4 and 601.33, the applicant may consult with the agency on how to establish effectiveness.

Proposed §§ 315.5(b) and 601.34(b) specify that the accuracy and usefulness of diagnostic information provided by a diagnostic radiopharmaceutical must be determined by comparison with a reliable assessment of actual clinical status. To obtain such a reliable assessment, a diagnostic standard or standards of demonstrated accuracy must be used, if available. An example of such a standard is a tissue biopsy confirmation of a site of a diagnostic radiopharmaceutical localization. If an accurate diagnostic standard is not available, the actual clinical status must be established in some other manner, such as through patient followup.

FDA intends to develop a guidance document that will provide more detailed guidance to industry on the types of clinical investigations that would meet regulatory requirements for obtaining approval for particular types of indications for diagnostic radiopharmaceuticals. The guidance may address such matters as appropriate clinical endpoints and suitable diagnostic standards. For indications that are common to multiple disease states, the guidance may address clinical trial design and statistical analysis considerations for patient populations that provide a range of representative disease processes.

F. Evaluation of Safety

FDA's proposed approach to the evaluation of the safety of diagnostic radiopharmaceuticals is set forth in §§ 315.6 and 601.35. Proposed §§ 315.6(a) and 601.35(a) state that the safety assessment of a diagnostic radiopharmaceutical includes, among other things, 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 adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

In §§ 315.6(b) and 601.35(b), FDA proposes that the assessment of the adverse reaction profile of a diagnostic radiopharmaceutical (including the carrier or ligand) include, but not be limited to, an evaluation of the product's potential to elicit the following: (1) Allergic or hypersensitivity responses, (2) immunologic responses, (3) changes in the physiologic or biochemical function of target and non-target tissues, and (4) clinically detectable signs or symptoms.

Proposed §§ 315.6(c)(1) and 601.35(c)(1) state that FDA may require, among other information, the following types of preclinical and clinical data to establish the safety of a diagnostic radiopharmaceutical: (1) Pharmacology data, (2) toxicology data, (3) a clinical safety profile, and (4) a radiation safety assessment. Other information that may be required to establish safety includes information on chemistry, manufacturing, and controls.

Under proposed §§ 315.6(c)(2) and 601.35(c)(2), the amount of new safety data required would depend on the characteristics of the diagnostic radiopharmaceutical and available information on the safety of the product obtained from other studies and uses. This information might include, but would not be limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide of the product, and results of preclinical studies on the product. Proposed §§ 315.6(c)(2) and 601.35(c)(2) further states that FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics that relate to safety risk and will specify the amount and type of safety data appropriate for each category. The paragraph states, as an example, that required safety data would be limited for diagnostic

radiopharmaceuticals with well-established low-risk profiles.

Proposed §§ 315.6(d) and 601.35(d) discusses the radiation safety assessment that will be required for a diagnostic radiopharmaceutical. FDA proposes that the applicant for approval of a diagnostic radiopharmaceutical establish the radiation dose of the product by radiation dosimetry evaluations in humans and appropriate animal models. Such evaluations must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. FDA notes that the use of occupational radiation dosimetry limits is not required in performing such evaluations. The maximum tolerated dose of the diagnostic radiopharmaceutical need not be established.

FDA intends to provide guidance on safety assessments for diagnostic radiopharmaceuticals. Such guidance may include a classification of diagnostic radiopharmaceuticals based on quantity administered, adverse event profile, and proposed patient population. The guidance would allow the safety information required to meet regulatory requirements to vary according to the class of the radiopharmaceutical. The guidance will also address evaluations of radiation dosimetry.

III. Analysis of Economic Impacts

FDA has examined the impact of the proposed 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. 104–114). 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 proposed rule and has determined that the rule is consistent with the principles set forth in the Executive Order and in these two statutes. FDA finds that the rule will not be a significant rule under 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 proposed 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 in order for the agency to properly evaluate the safety and effectiveness of new drugs or biological products. Such information is usually submitted as part of a new drug application (NDA) or biological license application or as a 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 proposed 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 proposed regulation may reduce the amount of safety information that must be obtained 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 proposed 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 in vitro and in vivo diagnostic substances 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 proposed rule would not impose any additional costs but, rather, is expected to reduce costs for manufacturers of certain diagnostic radiopharmaceuticals, as discussed previously. 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.

IV. Proposed Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 30 days after the date of its publication in the **Federal Register**.

V. Environmental Impact

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

VI. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is 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.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

[1] Medical and Healthcare Marketplace Guide, Dorland's Biomedical, sponsored by Smith Barney Health Care Group, 13th ed., 1997 to 1998.

Title: Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring.
Description: FDA is proposing regulations for the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring. The proposed rule would clarify 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 in primarily at 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 new biological license application 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 new drugs and antibiotics are set out in § 314.50 and for new biological products in § 601.25. Under the proposed regulation, information required under the act and the PHS Act and needed by FDA to evaluate safety and effectiveness would still need to be reported.
Description of Respondents: Manufacturers of in vivo radiopharmaceuticals used for diagnosis and monitoring.

To estimate the potential number of respondents that would submit applications or supplements for diagnostic radiopharmaceuticals, FDA used the number of approvals granted in fiscal year 1997 (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 referred to in the proposed regulations. The time needed to prepare a complete application is estimated 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 proposed regulations. The proposed rule would not impose any additional reporting burden beyond the estimated current burden of 2,000 hours because safety and effectiveness information is already required by preexisting regulations (parts 314 and 601). In fact, clarification by the proposed regulation 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. 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. FDA invites comments on this analysis of information collection burdens.

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.

Interested persons and organizations may submit comments on the information collection requirements of this proposed rule by June 22, 1998, to Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

At the close of the 30-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of the proposed rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions. 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.

VII. Request for Comments

Interested persons may, on or before August 5, 1998, submit to the Dockets Management Branch (address above) written comments on this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 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 Modernization Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR chapter I be amended 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, 356, 357, 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 shall 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 shall include 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.

(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 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 will vary 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 the ability to locate and characterize normal anatomical structures.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating 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 shall be 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 shall 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: The radiation dose; the pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand; the risks of an incorrect diagnostic determination; the adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

(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 non-target tissues.

(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.

(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 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 preclinical studies. FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data appropriate for each category. For example, for a category of radiopharmaceuticals with a well-established low-risk profile, required safety data will be limited.

(d) The radiation safety assessment shall establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. 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: 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; 15 U.S.C. 1451–1461; 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 *Samples for each importation* 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 amended by revising the title and adding §§ 601.30 through 601.35 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 shall be evaluated taking into account each intended use.

§ 601.31 Definition.

For purposes of this subpart, 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 shall include 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.

(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 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 will vary depending upon the proposed indication and may use one or more of the following criteria:

(1) The claim of structure delineation is established by demonstrating the ability to locate and characterize normal anatomical structures.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating 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 shall be 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 shall 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: The radiation dose; the pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand; the risks of an incorrect diagnostic determination; the adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

(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 non-target tissues.

(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.

(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 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 preclinical studies. FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data appropriate for each category. For example, for a category of radiopharmaceuticals with a well-established low-risk profile, required safety data will be limited.

(d) The radiation safety assessment shall establish the radiation dose of a

diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. The maximum tolerated dose need not be established.

Dated: April 15, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–13797 Filed 5–20–98; 11:44 am]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 89

[FRL–6014–4]

RIN 2060–AH65

Control of Emissions of Air Pollution from New CI Marine Engines at or Above 37 Kilowatts

AGENCY: Environmental Protection Agency (EPA).

ACTION: Advance notice of proposed rulemaking.

SUMMARY: EPA is issuing this Advance Notice of Proposed Rulemaking (ANPRM) to invite comment from all interested parties on EPA's plans to propose emission standards and other related provisions for new propulsion and auxiliary marine compression-ignition (CI) engines at or above 37 kilowatts (kW). This action supplements an earlier action for these engines initiated as part of an overall control strategy for new spark-ignition (SI) and CI marine engines (Notice of Proposed Rulemaking (NPRM) published November 9, 1994, modified in a Supplemental Notice of Proposed Rulemaking (SNPRM) published at February 7, 1996). The engines covered by today's action are used for propulsion and auxiliary power on both commercial and recreational vessels for a wide variety of applications including, but not limited to, barges, tugs, fishing vessels, ferries, runabouts, and cabin cruisers. This document does not address diesel marine engines rated under 37 kW, which are included in a proposed rulemaking for land-based nonroad CI engines published at September 24, 1997.

DATES: EPA requests comment on this ANPRM no later than June 22, 1998. Should a commenter miss the requested deadline, EPA will try to consider any comments received prior to publication of the NPRM that is expected to follow this ANPRM. There will also be opportunity for oral and written comment when EPA publishes the NPRM.

ADDRESSES: Materials relevant to this action are contained in Public Docket A–97–50, located at room M–1500, Waterside Mall (ground floor), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. The docket may be inspected from 8:00 a.m. until 5:30 p.m., Monday through Friday. A reasonable fee may be charged by EPA for copying docket materials.

Comments on this notice should be sent to Public Docket A–97–50 at the above address. EPA requests that a copy of comments also be sent to Jean Marie Revelt, U.S. EPA, 2565 Plymouth Road, Ann Arbor, MI 48105.

FOR FURTHER INFORMATION CONTACT: Margaret Borushko, U.S. EPA, Engine Programs and Compliance Division, (734) 214–4334.

SUPPLEMENTARY INFORMATION:

I. Purpose and Background

A. Purpose

Ground level ozone levels continue to be a significant problem in many areas of the United States. In the past, the main strategy employed in efforts to reduce ground-level ozone was reduction of volatile organic compounds (VOCs). In recent years, however, it has become clear that NO_X controls are often a more effective strategy for reducing ozone. As a result, attention has turned to NO_X emission controls as the key to improving air quality in many areas of the country. Building on the emission standards for CI engines promulgated in the early 1990s, EPA has recently promulgated a new emission control program for on-highway CI engines and proposed a new program for nonroad CI engines.[1, 2] Both of these programs contain stringent standards that will greatly reduce NOx emissions from these engines.

Similarly, particulate matter (PM) is also a problem in many areas of the country. Currently, there are 80 PM–10 nonattainment areas across the U.S. (PM–10 refers to particles less than or equal to 10 microns in diameter). PM, like ozone, has been linked to a range of serious respiratory health problems. Levels of PM caused by mobile sources are expected to rise in the future, due to the predicted increase in the number of individual mobile sources. Both of the new emission programs referred to above, for on-highway and nonroad CI engines, are anticipated to reduce ambient PM levels, either through a reduction in directly emitted particulate matter or through a reduction in indirect (atmospheric) PM formation caused by NO_X emissions.

Domestic and ocean-going CI marine engines account for approximately 4.5 percent of total mobile source NOx emissions nationwide. However, because of the nature of their operation, the contribution of these engines to NO_X levels in certain port cities and coastal areas is much higher. To address these emissions, today's action outlines a control program for CI marine engines at or above 37 kW that builds on EPA's programs for on-highway and land-based nonroad diesel engines identified above, EPA's recent locomotive rule, discussed below, and the International Convention on the Prevention of Pollution from Ships (MARPOL 73/78), Annex VI—Air Pollution developed by the International Maritime Organization (IMO).[3] If the emission standards and other requirements for those CI marine engines that use the same technologies reflected in EPA's on-highway, land-based nonroad, or locomotive rules are implemented as discussed in today's action, EPA would expect to see NO_X and PM reductions on a per-engine basis comparable to those achieved by engines subject to those rules. The numerical levels that EPA is considering applying to very large CI marine engines were intended by IMO to result in a 30 percent NO_X reduction. EPA continues to investigate IMO's anticipated reductions for those engines, based on the age and other characteristics of the U.S. fleet.

B. Statutory Authority

Section 213(a) of the Clean Air Act (CAA) directs EPA to: (1) conduct a study of emissions from nonroad engines and vehicles; (2) determine whether emissions of carbon monoxide (CO), oxides of nitrogen (NO_X), and volatile organic compounds (VOCs, including hydrocarbons (HC)) from nonroad engines and vehicles are significant contributors to ozone or CO in more than one area which has failed to attain the national ambient air quality standards (NAAQS) for ozone or CO; and (3) if nonroad emissions are determined to be significant, regulate those categories or classes of new

[1] In this notice, the term ''land-based nonroad'' and ''nonroad'' refers to the land-based CI engines and equipment regulated under 40 CFR part 89. It does not include locomotive engines.

[2] *See* 62 FR 54694 (October 21, 1997) and 62 FR 50152 (September 24, 1997).

[3] A copy of MARPOL 73/78 Annex VI and the associated NO_X Technical Code is available in this docket.