

§ 315.4

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

21 CFR Ch. I (4–1–03 Edition)

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 316—ORPHAN DRUGS

Subpart A—General Provisions

Sec.

- 316.1 Scope of this part.
- 316.2 Purpose.
- 316.3 Definitions.
- 316.4 Address for submissions.

Subpart B—Written Recommendations for Investigations of Orphan Drugs

- 316.10 Content and format of a request for written recommendations.
- 316.12 Providing written recommendations.
- 316.14 Refusal to provide written recommendations.

Subpart C—Designation of an Orphan Drug

- 316.20 Content and format of a request for orphan-drug designation.
- 316.21 Verification of orphan-drug status.
- 316.22 Permanent-resident agent for foreign sponsor.
- 316.23 Timing of requests for orphan-drug designation; designation of already approved drugs.
- 316.24 Granting orphan-drug designation.
- 316.25 Refusal to grant orphan-drug designation.
- 316.26 Amendment to orphan-drug designation.
- 316.27 Change in ownership of orphan-drug designation.
- 316.28 Publication of orphan-drug designations.
- 316.29 Revocation of orphan-drug designation.
- 316.30 Annual reports of holder of orphan-drug designation.

Subpart D—Orphan-drug Exclusive Approval

- 316.31 Scope of orphan-drug exclusive approval.
- 316.34 FDA recognition of exclusive approval.
- 316.36 Insufficient quantities of orphan drugs.

Subpart E—Open Protocols for Investigations

- 316.40 Treatment use of a designated orphan drug.

Subpart F—Availability of Information

- 316.50 Guidance documents.
- 316.52 Availability for public disclosure of data and information in requests and applications.

AUTHORITY: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

SOURCE: 57 FR 62085, Dec. 29, 1992, unless otherwise noted.

Subpart A—General Provisions

§ 316.1 Scope of this part.

(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:

- (1) Submissions to FDA of: