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July 1, 1998

BY HAND DELIVERY

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Re: Diagnostic Radiopharmaceutical Guideline

Dear Dr. Devine:

On behalf of the Council on Radionuclides and Radiopharmaceuticals (CORAR), I have enclosed a revised proposal for a "Guidance for the Development of Diagnostic Radiopharmaceuticals." CORAR submitted its initial proposed guidance to Docket No. 98N-0040 (Regulations for *In Vivo* Radiopharmaceuticals Used for Diagnosis and Monitoring) on May 21, 1998, indicating in the cover letter that CORAR might wish to revise its proposed guidance following the publication of FDA's proposed regulation relating to *in vivo* radiopharmaceuticals for diagnosis and monitoring. FDA's proposed regulation was published in the Federal Register the following day. 63 Fed. Reg. 28301 (May 22, 1998).

In response to several of the safety-related provisions of FDA's proposed regulation, CORAR has expanded the classification section of its proposed guidance (Section III.A at new pages 6-9). For example, FDA's proposal states 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 product obtained from other studies and uses." Prop. § 315.6(c)(2). This statement prompted CORAR to revise its proposed guidance to specify the kinds of information that should be submitted by a sponsor in a request for a Class 1 designation, including available information from other studies and uses (see new pages 7-8). In particular, where a diagnostic radiopharmaceutical has been previously approved for other uses, this information would include published and unpublished reports and a summary of adverse event data pertaining to the previously approved indication. However, where the radiopharmaceutical has not been previously approved but a carrier or ligand used in the

98D-0372

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PROPOSED
GUIDANCE FOR THE DEVELOPMENT
OF DIAGNOSTIC RADIOPHARMACEUTICALS

Submitted By

COUNCIL ON RADIONUCLIDES AND RADIOPHARMACEUTICALS, INC.
(CORAR)

July 1, 1998

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I. INTRODUCTION

Radiopharmaceuticals used for diagnostic imaging procedures are referred to as tracers because of the very small or trace amounts of material that are needed for diagnostic purposes. Radiopharmaceuticals can be elements that are themselves radioactive and are targeted to specific biochemical or physiological processes or to functional areas of the body. Radiopharmaceuticals can also consist of a combination of an extremely small amount of a pharmaceutical that is specifically targeted to a particular region or function of the body, and a radioactive element with which the pharmaceutical has been "tagged," usually technetium-99m. The pharmaceutical is generally administered at levels that do not elicit any clinically relevant pharmacologic responses since its only purpose is to deliver the radioactivity to the target. Once delivered to its specific site, the radioactive component of the diagnostic radiopharmaceutical provides a detectable signal as it collects in the area of interest.

Generally, diagnostic radiopharmaceuticals are used along with other clinical data to provide information on anatomy, physiology, biochemistry, function or pathology, allowing the physician to assess a patient and decide upon a final diagnosis or treatment plan. Rarely are diagnostic radiopharmaceuticals used alone to diagnose a specific disease. Typically, the physician will incorporate other clinical data and pertinent information into the decision tree. Accordingly, the Agency recognizes that it may be inappropriate, in many instances, for the labeled indication(s) of an agent to refer to one or more specific diseases. Such restrictive labeling prevents the practitioner from receiving comprehensive information about the full potential clinical uses of the imaging agent. In addition, limiting diagnostic radiopharmaceuticals to disease-specific indications would theoretically require a separate clinical trial to support each labeled disease state and could potentially impose on the sponsor the burden of conducting unnecessary clinical trials.

Diagnostic radiopharmaceuticals are under development for a wide range of indications, including anatomical/structural delineation, organ function assessment, non-specific tissue identification, and tissue function assessment on the basis of a metabolic process and cellular

receptor-specific localization. Diagnostic radiopharmaceuticals may also be used in specific treatment planning, to predict disease and treatment outcomes and to guide patient management practices, as well as for indications that are based upon cost and usage comparisons or pharmacoeconomic models.

The development of diagnostic radiopharmaceuticals is guided by consideration of data that include (but are not limited to):

Chemical characteristics
Dose (radiation and chemical)
Route of administration
Metabolism and route of excretion
Half-life (physical and biological)
Mechanism(s) of action
Effectiveness
Frequency of use
Side effect profile
Intended use

The purpose of this document is to offer guidance for the development of diagnostic radiopharmaceuticals. These points are not all-inclusive. Alternative approaches may be suitable in specific situations, and certain aspects may not be applicable to all situations. This document has been prepared to assist sponsors in planning clinical evaluations of diagnostic radiopharmaceuticals, in preparation for submission of a New Drug Application (NDA), a Supplemental NDA (sNDA), or a Biological License Application (BLA). This document supersedes "Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs." In addition to this document, sponsors should consult and become familiar with 21 C.F.R., parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), 201 (Labeling), 312 (Investigational New Drug Application), 314 (Applications for FDA Approval to Market a New Drug or an Antibiotic Drug), and 600 (Biological Products). In addition, the sponsor may wish to consult "General Considerations for the Clinical Evaluation of Drugs," "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and

Biological Products" (draft guidance release for comment on March 13, 1997), and other pertinent guidelines available from the Agency.

The Federal Food, Drug, and Cosmetic Act mandates that, in order to receive approval for marketing, new drugs must be demonstrated to be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling. This document describes the types of indications appropriate for diagnostic radiopharmaceuticals, the appropriate methods for determining efficacy for each type of indication, and the types of data appropriate for determining the safety of diagnostic radiopharmaceuticals.

II. INDICATIONS

A. INTRODUCTION

Efficacy of a diagnostic radiopharmaceutical may be expressed as its ability to provide information that contributes to a patient's diagnosis or treatment (e.g., facilitated visualization of lesions/structures or normal/abnormal blood flow), or alternatively, as the diagnostic performance of the agent (e.g., sensitivity and specificity).

In certain cases, the efficacy of a diagnostic radiopharmaceutical can be demonstrated by evaluating the agent's sensitivity and specificity as a diagnostic or prognostic marker of a certain disease versus an appropriate comparator. Although this approach is appropriate where the relationship between the parameter being imaged and the disease process is well established, or where there is a specific criterion to define the disease (e.g., coronary artery disease and abnormal coronary angiography), this approach may have less relevance when the parameter being measured relates to a common function or biochemical status of the organ or tissue in multiple diseases (e.g., regional glucose utilization in the brain is disrupted in a number of different neurological diseases). In the latter case, the diagnostic performance of the radiopharmaceutical may be characterized by good sensitivity and less robust specificity by disease, but excellent sensitivity and specificity for a biochemical/functional process. Although functional or biochemically targeted diagnostic radiopharmaceuticals may provide only limited information about disease specificity, these agents may still provide valuable insight into the

extent and severity of disease which could not otherwise be obtained. Since biochemical and functional abnormalities often precede alterations in tissue morphology, an early understanding of the pathological process could be critical to patient management. Therefore, multiple indication categories are appropriate for diagnostic radiopharmaceuticals. Indications for diagnostic radiopharmaceuticals can be categorized into the following non-exclusive groups:

Structural Localization
Functional Assessment
Biochemical Characterization
Disease Specific
Management Decision Making

These indication groups are described in turn below.

B. SPECIFIC INDICATION GROUPS

Structure Localization

Examples of this type of indication are the delineation of the gastrointestinal tract or the enhancement of a vessel. The primary requirement for this type of indication is that the agent must be able to locate and characterize the structure. A secondary requirement, depending on the indication sought, is that the images of the agent must be able to distinguish between a normal and abnormal appearance of the particular structure (i.e., characterization of disease-dependent alterations in the structure). Depending on the structure to be localized and the intended purpose for localization, comparisons to comparator products or procedures may provide adequate data to support a proposed indication. The sponsor should communicate with the Agency and obtain agreement on the expectations for documentation of the performance of the agent and whether a normal subject cohort is needed with the patient cohort.

Functional Assessment

Examples of this type of indication are the characterization of ejection fraction, myocardial wall motion or cerebral perfusion. Functional indications focus on determining if the parameter

assessed is within normal limits and thus includes qualitative, semi-quantitative or quantitative parameters and knowledge of their normal range and/or distribution.

Biochemical Characterization

Examples of this type of indication are the use of a marker for glucose utilization or a labeled antibody or peptide that recognizes a specific type of receptor. The biochemical characterization indication focuses on determining if the parameter assessed is within normal limits, with respect to the presence of, amount of, and/or distribution of the receptor. This type of indication requires that a qualitative, semi-quantitative or quantitative understanding of the parameter is known, along with the variability for that parameter in normal tissue. Acceptable evidence that a particular biochemical process can be characterized with the diagnostic radiopharmaceutical includes, but is not limited to, pharmacologically induced perturbations of the system to be measured (e.g., administration of a specific receptor antagonist which results in altered tracer binding), or *in vivo/in vitro* analysis (e.g., tissue autoradiography). Full biochemical documentation in at least one acceptable animal species is the minimum non-clinical requirement for approval of this type of indication (e.g., autoradiography of rat brain for a central nervous system receptor agent). Performance measures could reflect accuracy, precision, and minimum detectable limits of the quantitative or semi-quantitative measurement.

The use of a diagnostic radiopharmaceutical to target marker substances, such as hormones, enzymes, or antigens, altered by a disease are also included in this category. For example, where several types of tumors express or over express a similar marker, such as chorionic gonadotropin, alpha-fetoprotein, carcinoembryonic antigen, or certain ectopic enzymes, a diagnostic radiopharmaceutical, such as an antibody against such a marker or fluorodeoxyglucose (FDG), may contribute to the diagnosis or monitoring of the multiple diseases that express these markers. In such cases, it is not necessary to conduct studies in each disease or tumor type that abnormally expresses the abnormal or ectopic marker.

Disease Specific

Examples of this type of indication are the use of a monoclonal antibody for the detection of a tumor subtype or of various organs having inflammatory reactions or cell-specific reactions to infection, or the use of labeled cells or antibodies for the detection of infection or thrombus. These types of indications would result in general disease-specific claims and would require clinical trials to determine the sensitivity and specificity of the imaging agent to identify, demonstrate, or detect the disease, without requiring an organ-by-organ restricted clinical trial and indication.

Management Decision Making

Examples of this type of indication are the assessment of the prognostic value of the diagnostic radiopharmaceutical test to predict post-revascularization outcome in patients with coronary artery disease, or the evaluation of the resectability of a patient with recurrent colorectal carcinoma, or a determination of the extent of disease. These types of indications result in information leading directly to a patient management decision and focus on clinical trials to assess the impact of the imaging test on management decisions and on the outcomes of those management decisions. A management decision making indication may specify that the diagnostic radiopharmaceutical is to be used in conjunction with other tests to affect a patient management decision.

III. TRIAL DESIGN

A. CLASSES OF DIAGNOSTIC RADIOPHARMACEUTICALS

Diagnostic radiopharmaceuticals fall into two classes for purposes of determining the data necessary to establish safety and optimal dose. Class 1 consists of diagnostic radiopharmaceuticals that are administered at tracer quantity levels and have demonstrated negligible potential for eliciting a clinically significant response or an unintended pharmacologic

response. The majority of traditional diagnostic radiopharmaceuticals are Class 1. Class 2 consists of diagnostic radiopharmaceuticals that do not qualify for inclusion in Class 1.

At any point in the clinical development of a diagnostic radiopharmaceutical, the sponsor may submit a request to FDA for designation of the radiopharmaceutical as Class 1. FDA will designate an agent as a Class 1 diagnostic radiopharmaceutical if the sponsor submits preclinical data, clinical data, and/or other information demonstrating that the agent meets the above definition of Class 1. A sponsor may request Class 1 designation for a previously unapproved diagnostic radiopharmaceutical or for a new indication for a previously approved diagnostic radiopharmaceutical.

In determining whether a diagnostic radiopharmaceutical qualifies for a Class 1 designation, FDA will take into the account the following:

(1) The dose (both mass and radioactive dose).

(2) The frequency of administration.

(3) The proposed patient population.

(4) The results of nonclinical toxicity and pharmacology tests.

(5) The clinical adverse event profile of the diagnostic radiopharmaceutical (where such information is available).

(6) The clinical adverse event profile of the carrier or ligand used in the radiopharmaceutical where essentially the same carrier or ligand has been used in other commercially marketed products (e.g., non-radioactive products and/or products for therapeutic use).

In support of a request for Class 1 designation, the sponsor should submit the following information:

(a) A description of the diagnostic radiopharmaceutical and a discussion of the scientific rationale for its use for the proposed indication.

(b) A summary of the results of all nonclinical and clinical studies conducted by the sponsor on the diagnostic radiopharmaceutical, and/or on the carrier or ligand (if any) that is a component of the diagnostic radiopharmaceutical.

(c) Pertinent published or unpublished reports on the diagnostic radiopharmaceutical, or on the carrier or ligand that is a component of the diagnostic radiopharmaceutical.

(d) Where a diagnostic radiopharmaceutical has been previously marketed in the U.S. for another indication or has been marketed in other countries, a summary of adverse event information relating to the diagnostic radiopharmaceutical.

(e) Where a carrier or ligand that is a component of the diagnostic radiopharmaceutical has been used in products previously marketed in the U.S. or other countries, a summary of adverse event information relating to the carrier or ligand.

(f) A summary explanation of why the radiopharmaceutical has demonstrated a negligible potential for eliciting a clinically significant response or unintended pharmacological response.

FDA will make a determination whether to designate a diagnostic radiopharmaceutical as Class 1 as soon as practicable after the sponsor submits a request. Although it is the sponsor's responsibility to request a Class 1 designation, FDA may, on its own initiative, suggest to a sponsor that a diagnostic radiopharmaceutical is eligible for Class 1 designation based on data submitted by the sponsor or based on the Agency's previous experience with other similar products or with the carrier of ligand that is used in the diagnostic radiopharmaceutical.

Biological materials that are administered at tracer quantity levels but have the demonstrated potential for eliciting a clinically significant immunologic-type response, and agents that are administered at mass levels where the potential for a clinically relevant pharmacological

response is theoretically possible, are Class 2 agents. Classes 1 and 2 present different considerations with respect to optimal dosage and requirements for demonstrating safety. These differences are discussed as appropriate in the remainder of this document.

B. PRECLINICAL/NONCLINICAL STUDIES

Preclinical studies should be designed to assess the safety and initial pharmacodynamic parameters of the drug formulation at various doses, when appropriate, in suitable animal models. Additional studies in animal models of organ functional impairment (e.g., impaired renal, hepatic, or cardiac function) may be needed depending on the findings in normal animals. The effects of misadministration should be evaluated in a manner that is appropriate for the intended route of administration. For example, in the case of a diagnostic radiopharmaceutical intended for intravenous administration, extravasation effects should be evaluated. Physical incompatibilities of the drug with syringes, intravenous tubing, intravenous solutions, etc., should also be assessed. Preclinical and nonclinical studies should additionally determine radiation absorbed doses to various body tissues. The extent of the nonclinical testing required for a diagnostic radiopharmaceutical will depend on the class of the agent. Class 1 agents can undergo reduced nonclinical testing because of their inherent safety profile. For example, Class 1 diagnostic radiopharmaceuticals will not routinely require long term, multi-dosing subchronic/chronic toxicity studies, carcinogenicity studies and reproduction studies.

C. CLINICAL STUDIES - PHASES

Phase I Studies

The goals of Phase I studies include safety and pharmacodynamics, but may also include early assessments of efficacy. Distribution data over time should be collected for the calculation of radiation dosimetry. The population sample may be apparently healthy subjects or patients, depending on the diagnostic radiopharmaceutical's mechanism of action. Females may be used,

but there should be a determination of risk/benefit for female patients of childbearing potential. Use of female patients is not mandatory except for those diseases/pathologies that are unique to females, e.g., ovarian cancer.

Experience in Phase I may be used to justify or confirm a Class 1 designation. To support a Class 1 designation, the results of testing in Phase I must demonstrate that there are no clinically significant responses or unintended pharmacologic effects that are attributable to the radiopharmaceutical under investigation. For example, there should not be any clinically significant increases in enzyme levels associated with the test agent. Moreover, the results in Phase I must be consistent with the results obtained during the nonclinical testing portion of the drug development process. At the end of Phase I, the results should demonstrate that the pharmacologic parameters and the patient dosimetry are acceptable and consistent with all previously gathered preclinical/nonclinical data.

Phase II Studies

The goal of Phase II studies is generally to confirm the dose and to obtain a preliminary evaluation of efficacy, with the aim of choosing from several doses the one with the most favorable risk-benefit balance for those diagnostic radiopharmaceuticals with pharmacological activity. The same methods that will be used for data analysis in Phase III should be used in Phase II whenever possible. Sample sizes must consider appropriate statistical factors. The same patient population that will be studied in Phase III should be studied in Phase II. Proof of concepts or preliminary efficacy questions about the drug should be explored in Phase II. This is particularly true for agents (such as FDG) for which there may be many potential uses, based upon their mode of action, but for which inadequate animal models exist to test the concept.

Phase III Studies

The goal of Phase III studies is to provide sufficient data to demonstrate the safety and efficacy of the agent. Sample sizes employed in Phase III trials should be appropriately powered to allow

for a reasonable determination of drug performance and safety based on statistical principles. Phase III trials should incorporate the final formulation that will be marketed, whenever possible, since the information resulting from Phase III will be included in the labeling (package insert) for the drug. The effectiveness of a diagnostic radiopharmaceutical (e.g., diagnostic evaluation of images, or sensitivity/specificity) is established in Phase III. The phases of clinical development may overlap, such as Phase II/III.

D. CLINICAL STUDIES - DOSAGE DETERMINATION

Unlike therapeutic drugs, which generally accomplish their intended effect by pharmacologic action through the mass administered, diagnostic radiopharmaceuticals typically achieve their intended effect due to the radioactivity administered. For Class 1 radiopharmaceuticals the mass injected is, by definition, subpharmacologic, but for Class 2 radiopharmaceuticals both types of dose - mass and radioactivity - must be considered.

Establishment of an effective dose may begin with preclinical studies and may include studies in both animals and *in vitro* phantoms. In these studies, a concentration or possibly a range of concentrations may be shown to produce the desired clinically useful result. Often these studies are completed and are included in the original IND submission. Together with preclinical toxicity studies, they form the basis for dose range selection in the Phase I studies.

An effective dose for a diagnostic radiopharmaceutical may be determined in Phase I or Phase II trials (dose ranging studies should span the projected dose range to be used clinically) and should establish the lowest efficacious dose or a dose that is within acceptable risk benefit criteria. As many diagnostic radiopharmaceuticals are well tolerated at all mass dose levels tested, it is not usually necessary, or even possible, to establish a maximally tolerated (mass) dose (MTD). When developing a therapeutic agent, the (mass) MTD sets a ceiling to be considered when the dose needs to be increased to reach the "desired" efficacy. To the extent that there is a dose response for an imaging agent, and the maximally efficacious dose is well tolerated, there is no real value in determining the (mass) MTD. However, agents that have a high probability of

repeat exposures should be investigated to determine whether a maximally tolerated exposure limit might exist.

Because of the mechanism of action of diagnostic radiopharmaceuticals, the optimal time of imaging is as important a consideration as the optimal dosage. Organ distribution and washout information will generally establish a theoretically ideal imaging time. The time window of effective imaging (i.e., how soon after administration and for how long) should be established.

Final dose selection is part of an assessment of risk/benefit. Does an increase in dose provide a substantial or proportional increase in image quality, a longer imaging window, a shorter study time (for unstable patients) or an increase in additional information? It may be possible for such an assessment to be made in a limited number of patients by investigators who are evaluating the diagnostic radiopharmaceutical in the manner in which it is intended to be used in clinical practice.

Independent image review by reviewers blinded to all clinical information may not be necessary. The sponsor should discuss with the Agency the principle used to determine the comparability, superiority or inferiority of different doses. This may include evaluation of qualitative assessments, quantitative measures, presence or absence of artifacts, and versatility of the selected dose over a variety of equipment in those instances where specific equipment is critical to the performance of the diagnostic radiopharmaceutical. These principles should be documented and systematized whenever possible. The dose-dependent risks from exposure to the product (e.g., pharmacological risk, radiation risk, etc.) must be balanced with the benefit of an acceptable image or sensitivity for detection by radiation-detecting probes.

In the absence of a significant pharmacologic effect, diagnostic radiopharmaceutical doses are generally established based on the radiation dosimetry data generated during Phase I clinical studies. The maximal dose of a radiopharmaceutical is generally based on the amount of radiation the patient will absorb and not on pharmacological action or adverse events associated

with the imaging agent, both of which are usually negligible. There is no single, generally applicable limit to the amount of radiation a patient should receive. Occupational exposure levels (e.g., 5 rads to a critical organ) are not necessarily appropriate. The radioactive dose rather should be based on an assessment of risks versus benefits, as discussed above. For Class 1 radiopharmaceuticals, dose-ranging studies may not be necessary. For these types of agents, the lower limit of the dosage range may be established based on mathematical and/or physical models (i.e., phantoms) with the upper limit based on acceptable radiation dosimetry estimates. For Class 2 diagnostic radiopharmaceuticals, an additional dosage consideration is the specific activity of the product. For Class 2 agents with a potential for antigenic response, the lowest protein dose with the highest radioactive dose (i.e., high specific activity) may be a typical development goal. For diagnostic radiopharmaceuticals administered at mass quantities that may elicit a significant pharmacologic effect, such as receptor agents, the upper dosage limit is the mass dosage that could potentially elicit a clinically observable pharmacological response and the lower dosage limit is the minimum radioactivity dosage needed for a satisfactory image. The relationship between the mass dose and the radioactivity dose will be determined by the achievable specific activity for the product.

E. CLINICAL STUDIES - APPROACH TO TRIAL DESIGN

The traditional therapeutic agent type of approach to trial design is applicable to the "disease specific" indication of a diagnostic radiopharmaceutical. In this approach, the primary analysis relates to disease or no disease, and clinical studies focus on the efficacy and safety of a diagnostic radiopharmaceutical in detecting and/or characterizing one particular disease (e.g., lung cancer). The advantage of this approach is that well-defined subject selection criteria can be identified, and maximum information can be obtained in a relatively homogeneous population.

As discussed in Section II, in addition to the generally recognized disease-specific indication, approval of a diagnostic radiopharmaceutical may also be based on its ability to detect abnormalities in structure, function or biochemistry (i.e., an ability to distinguish normal from abnormal). In the latter paradigm, the safety and efficacy of the diagnostic radiopharmaceutical

in detecting and/or characterizing a pathophysiologic process or mechanism (e.g., ischemia) is studied. Such a process may be common to two or more clinical diseases, and may be detectable in the subclinical phase of disease.

Two possible alternative clinical trial design paradigms that support pathophysiologic indications for diagnostic radiopharmaceuticals are the model approach and the multiple small cohort approach. In each case, the primary analysis is normal versus abnormal, in contrast to a disease-specific indication, where the primary analysis relates to the presence or absence of disease. Therefore, the key to data analysis, in most cases, is to include a cohort of normal subjects or tissue to establish "normal" performance for the diagnostic radiopharmaceutical being studied. An exception to the normal versus abnormal scenario would be, for example, regional anaerobic glycolysis in a tumor for which there is no "normal" tumor.

Model Approach

Using the model approach, the trial focuses on representative diseases that involve the biological processes for the indication that is being sought (e.g., altered wall motion, abnormal anatomy, or altered receptor density). The process would be extrapolated to other disease states based on the common process rather than the specific disease.

An example of an agent for which this approach would be potentially useful would be a product that localizes in or binds to specific types of cells. Multiple cellular events, from inward passage of selected nutrients to signaling by hormone molecules, depend upon interactions with the cell surface. Some molecules bind to a surface receptor while, in other cases, the molecule is internalized within the cell. The focus of these types of agents would be on the mechanism or process by which they bind to or are incorporated into a cell and not on a specific disease. The appropriate models would need to be selected on a case-by-case basis, and a justification given as to why any particular disease is included in the model of the process, and why the results obtained from that model can be extrapolated to other diseases.

Multiple Small Cohort Approach

This approach would allow for the *a priori* stratification of patients into specific cohorts (based on disease) as they are enrolled into the trial. As part of the trial design, the sponsor, concurrently with FDA, decides how many patients in each cohort will be evaluated. The primary analysis from this type of study is normal versus abnormal, and the secondary analysis is similar to the traditional disease-specific indication with sensitivity and specificity determined for each cohort.

The multiple small cohort approach provides versatility in trial design and data analysis. Moreover, it provides information on multiple disease states and estimates of sensitivity and specificity. This type of information can be provided in the "Clinical Trials" section of the package insert, and allows a clinician to make an informed decision on the best manner in which to use a new agent in the clinical setting. It is important that the sponsor discuss the clinical trial design with the Agency and that agreement be reached on the number of patients required for each cohort to permit the estimation of diagnostic statistics (i.e., sensitivity and specificity).

Example of Multiple Small Cohort Approach – Phase III:

Cerebrovascular Disease

Indication Sought: Indicated as a marker of cerebral blood perfusion

Comparison for Secondary Analysis: Final Diagnosis (all clinical information without the imaging study)

Total Patient Population: 225 patients/subjects

25 Normal Subjects

50* Stroke Patients

50* Head Trauma Patients

50* Dementia Patients

50* Seizure Patients

Primary Analysis: Detection of Cerebral Perfusion Defects - Normal vs. Abnormal combining all subjects and patients (225 subjects/patients).

Secondary Analysis: Disease Cohort (50 patients) vs. Normal Subjects (25 subjects). Include a comparison to final diagnosis (all available clinical information) allowing for the estimation of diagnostic statistics (i.e., sensitivity/specificity).

*Suggested minimum number of patients per Cohort is 50, assuming a minimum positive finding rate of 60% (i.e., n=30 positive disease per cohort). This should allow for reliable estimates of diagnostic statistics within reasonable confidence intervals.

F. CLINICAL STUDIES - CONFIRMATORY DATA

General Considerations

The primary efficacy question for any diagnostic radiopharmaceutical is whether it provides information that can assist in patient diagnosis or management. Therefore, there are two possible components to the efficacy issue:

(1) The correctness of the information provided by the diagnostic radiopharmaceutical; and
(2) The impact of that information on patient care (i.e., patient management), when appropriate.

The parameters acceptable for defining "patient management" impact would depend on the indication being sought. Only for the "Patient Management Decision-Making" indication would effecting a change in diagnosis or management be mandatory in order to prove that the agent is "effective." For the other types of indications discussed above (i.e., Structural Localization, Functional Assessment, Biochemical Characterization, or Disease Specific), efficacy would primarily be defined with respect to the performance characteristics of the agent. Whether the use of the agent alters a patient's diagnosis, prognosis, or staging, or has an impact on patient management, is not a consideration, or is only a secondary consideration, in these cases.

Information obtained from the administration of the agent may be complementary rather than equivalent or superior to information acquired from other standard diagnostic modalities. Where

standard diagnostic modalities exist, performance characteristics of the new agent should be compared to the standard and/or verified by another means when that standard appears to be imperfect. The value of the information determined from the diagnostic radiopharmaceutical (i.e., benefit) should be compared to the risks associated with exposure to the agent and the diagnostic modality and the risks associated with incorrect information. When either the standard diagnostic modality or the new agent pose significant risks (potential adverse effects or incorrect information), a comparative risk/benefit analysis needs to be performed.
Whenever possible, investigations should be designed to minimize bias (i.e., results of the administration of the test agent influencing the treatment algorithm). Where feasible and ethical, the results of the diagnostic test should be withheld from the clinician responsible for the management of the patient in order to ascertain the least biased measures of the appropriate diagnostic statistics.

Endpoints

Primary endpoints can be:

- functional endpoints (e.g., left ventricle ejection fraction, or LVEF);
- biochemical endpoints (e.g., receptor density);
- a pathophysiological process (e.g., the determination of lesion size or disease location);
- the number of lesions or extent of disease;
- the type of lesion/disease visualized; or
- characteristics of the detected disease (or a manifestation of the disease) or additional confidence in the diagnosis.

These endpoints may have clinical importance in the care of the patient. An important issue to be addressed in designing a clinical trial is the role of the test agent in obtaining a diagnosis for the patient. In some instances, the endpoint may supply unique information that is more reliable than other tests and has value in that it defines prognosis or prospects for future therapy. However, this does not mean that an agent must be better than agent(s) already commercially

available in order to gain FDA approval. The endpoint may be diagnostic equivalence to an existing test but with an improved safety profile, or the test agent may be more convenient to use, less invasive and/or provide better timing. Other measurable secondary endpoints, such as decreases in total study procedure time, could be used to support additional labeling claims.

Comparators - "Gold Standards"

Assessing the accuracy of the information determined from a diagnostic radiopharmaceutical study requires a judicious choice of a comparator agent or procedure, i.e., "gold standard." Gold standards themselves frequently may be diagnostic tests, and therefore also have a degree of uncertainty with respect to accuracy and precision. Certain gold standards are commonly used in clinical trials, but other appropriate gold standards may be possible depending on the diagnostic radiopharmaceutical and the proposed indication. Some potential gold standards for a diagnostic radiopharmaceutical clinical trial include:

- Histopathology
- Therapeutic response
- Clinical outcome
- Another approved diagnostic radiopharmaceutical
- Another diagnostic test, validated against a valid gold standard
- *In vitro* tests
- Animal autoradiography
- Autopsy

Direct observation of disease at surgery or via histopathology is generally considered a reasonable gold standard for knowing the true health state of the patient at a given point in time. However, there may be limitations because of differences in methodology or in definitions of a positive result. There may also be inherent selection and observer bias in the use of surgery and histopathology as gold standards, because generally only patients with positive test results (and patients thought to have false negative test results) are typically subjected to biopsy or surgery, for obvious ethical reasons. The appropriate gold standard must be chosen individually for each investigational drug and it is recommended that the Agency be consulted during study design to insure the acceptability of a the standard chosen.

Comparators - When No Approved Comparator Exists

When a suitable "gold standard" does not exist, comparisons may be made to an assessment of all available clinical information excluding information obtained with the test agent, i.e., final diagnosis or overall clinical impression.

Comparators - Comparison To An Approved Agent

In the event that the test agent is being developed for an indication for which another agent is currently approved, a direct, concurrent comparison to the approved agent may suffice as adequate evidence of efficacy for FDA approval. The comparison may be based on image characterization such as visualization of organs and/or pathology, determination of extent of pathology, measurement of signal intensity, or performance measures. Whenever possible, a paired study design (e.g., with the comparator and with the new agent) should be employed that allows for the subject to be his/her own control. In the cases where this design is not possible (e.g., ethical considerations due to radiation exposure), a parallel design using both agents concurrently should be employed. Because of the many potential confounding factors, historical controls should only be considered when alternative control designs cannot be employed. In these instances, the use of historical controls should be reviewed and discussed with the Agency.

Placebos

The use of placebos is not needed in the evaluation of the efficacy of diagnostic radiopharmaceuticals. The potential role of placebos in the evaluation of safety is discussed below.

Blinded Versus Unblinded Readers

For purposes of this section, "blinded" refers to an information-deficit state. A "blinded" reader is not an untrained or inexperienced reader. Two different, non-mutually-exclusive types of "blinding" exist. In the first type, agent blinding, the evaluator of an imaging study is "blinded"

to the identity or the dose of the imaging product (e.g., test agent versus comparator product) evaluated in a randomized controlled trial. In the second type, clinical blinding, the evaluator is provided with little or no patient-specific clinical information upon which to base or modify the image interpretation. The first type, agent blinding, is comparable to the traditional double-blind study employed for therapeutic agents. Agent blinding is useful to reduce bias when determining performance characteristics for the new agent compared to the comparator product and determining optimal dosages.

The second type, clinical blinding, is unique to imaging agents. Clinically blinded reader (BR) studies are used to evaluate efficacy data (content and information in the image alone) in a "worst-case scenario." This evaluation is conducted in a controlled setting with minimal or no clinical information provided to the reader. This environment is not representative of the conditions under which the test agent will ultimately be used clinically, but may provide important baseline performance information and reduce study bias. "Clinical blinding" is a relative concept. The specific information provided may depend on the modality under study, type of agent and/or proposed indication. The BR should be provided with sufficient information to provide an interpretation of the data without leading the reader to a specific determination. It may be appropriate to provide some demographic information such as age, sex, and weight, unless such information will introduce unacceptable BR bias. If the protocol enrolls patients for evaluation of a specific disease, (e.g., coronary artery disease), the BR should know this fact, but a selection of normal studies should be included in the blinded read to prevent bias and to provide some specificity data. Studies employing "sequential unblinding" (i.e., providing more and more clinical information to the reader) will provide information on the performance of the agent under the variety of conditions that may be encountered in routine clinical practice (i.e., when no clinical information is available, when limited clinical information is available, and when an appropriate amount of information is available).

The design of BR studies has evolved over the years. The current state of the art requires that multiple readers (at least two) be used for each clinical study. With multiple readers, there may

be points of disagreement between or among readers. Each reader provides a valid set of readings; information on accuracy, sensitivity and specificity (if appropriate) is valid for each reader. Methods to minimize inter-reader variability should be incorporated into the study design. Such methods can include training sessions, and differentiating between variability that results from differences in diagnoses versus variability that results from differences in medical practice (e.g., differences in severity of an abnormality may be clinically irrelevant in some settings, while leading to differences in medical management in others).

Efficacy need not be determined by the results of the blinded read alone. The clinical investigator's evaluation can be relied upon for the efficacy determination, with the blinded read serving as an independent assessment of the objectivity of the clinical investigator's results. The sponsor should analyze each type of data collected under each type of circumstance (blinded read and investigator's assessment) with respect to the appropriate indication.

G. SAFETY EVALUATIONS

Safety Evaluation Requirements for Diagnostic Radiopharmaceuticals

The safety profile of diagnostic radiopharmaceuticals differs significantly from that of most conventional drugs. Radiopharmaceuticals represent some of the safest compounds in use today. Radiopharmaceuticals differ from conventional drugs, both in characteristics and method of use, in several key ways:

- The carrier moiety is generally administered in extremely small quantities;
- The carrier moiety usually does not elicit clinically significant pharmacologic effects; and
- Diagnostic radiopharmaceuticals are usually given infrequently over a patient's lifetime.

In addition, the amount of radiation used is small and the isotopes used have relatively short half-lives.

Serious adverse events associated with radiopharmaceuticals are far more infrequent than those associated with conventional therapeutic drugs or other diagnostic imaging compounds. Because of the safety profile and pattern of use of radiopharmaceuticals, the extensive preclinical pharmacology/toxicology testing currently required of therapeutic drugs and conventional imaging agents (e.g., x-ray contrast agents) may be reduced for diagnostic radiopharmaceuticals in many cases, but not omitted.

The extent and kinds of safety testing required for a diagnostic radiopharmaceutical depend on its class.

Class 1: Class 1 agents are subject to more flexible, less exhaustive requirements for safety testing and dose range testing than Class 2 agents. Ordinarily, Class 1 agents will not require certain non-clinical toxicity studies (see section III.B, above), and will not require dose-ranging studies (see section III.D, above). In addition, Class 1 agents ordinarily will not require clinical trials in special populations (e.g., patients with cardiac or renal failure), nor extensive misadministration studies. Certain other types of safety testing may be unnecessary in a particular case. The kinds of safety testing required for a Class 1 agent should be discussed and agreed to between the FDA and the sponsor.

Safety evaluations for Class 1 diagnostic radiopharmaceuticals should focus primarily on the radiation dosimetry. Safety should be monitored in Phase I. Vehicles and adjuvants may have to be evaluated separately from the active ingredients. If the active ingredient poses minimal toxicological risk and the vehicle and carrier have a long history of safe use, minimal monitoring in Phase II and Phase III may be justified.

Class 2: Class 2 compounds which have the potential for eliciting immune-type responses must meet the testing requirements for Class 1 agents and, in addition, the risk of sensitization to the agent must be evaluated. Antibodies to the product (e.g., polypeptides) or to the type of antibody

(e.g., HAMA) should be evaluated. If the potential for multiple clinical exposures exists, "readministration" trials should be designed to evaluate the risk. Labeling should reflect the degree to which this question has been explored.

Class 2 agents that are administered at mass levels, where the potential for a clinically significant pharmacological response is theoretically possible, must also meet the testing requirements for Class 1 agents. Additional tests may be required based on the potential safety risks related to, for example, the type of receptor agent (i.e., agonists versus antagonists) or the mass quantity of agent to be administered. Therefore, the specific activity of the agent is critical in evaluating the potential risks. As a rule of thumb, agents that may be used for diagnostic purposes at dose levels less than 5% of the minimum dose required for an observable pharmacologic response pose minimal risks for pharmacological effects. For these agents, extensive safety evaluations should be conducted in a limited number of patients in Phase I. On the other hand, agents used at a dose level greater than 5% of the minimum dose level at which pharmacological effects are observed pose an increased risk of pharmacological effects. Therefore, more extensive safety evaluations would possibly be required for these agents.

Radiation dosimetry calculations must be performed for all radiopharmaceuticals. Dosimetry estimates should be based on comprehensive biodistribution data collected in at least one animal species and should later be confirmed in a limited number of human subjects.

Adverse Events

An adverse event is any detectable abnormality in a patient that was either not present prior to drug administration but was present following drug administration, or that was present prior to drug administration but worsened following drug administration. This includes symptoms, physical signs, vital signs, laboratory signs, electrocardiographic signs, etc. Therapeutic measures taken in response to adverse events are not considered adverse events (e.g., initiation or prolongation of hospitalization, surgery, or other therapeutic measures) but are medical responses to adverse events.

Adverse events may be due to the underlying disease, the anxiety of the patient, or the imaging procedure itself (e.g., the confined space and noise associated with a Single Photon Emission Computer Tomography, or SPECT, imaging scanner). Historical data concerning the rate and type of adverse events associated with a particular modality independent of the agent administered may be useful in defining the true adverse event profile for a particular agent.

Study Considerations

The use of a placebo may be helpful in the assessment of the safety of certain diagnostic radiopharmaceuticals. If a placebo is used, adverse events observed after the administration of the placebo may be used as an aid in differentiating procedure-related events from events caused by the test drug. Those events attributable to placebo may be described in the labeling. In cases where the proposed indication for the agent will likely involve imaging patients with high incidences of placebo responses (i.e., neurological and psychiatric disorders), an assessment of adverse events observed with placebo is warranted.

A safety evaluation is conducted throughout all phases of investigation, with the need for more stringent evaluations (e.g., hematology, serum chemistry, coagulation parameters, and urinalysis with microscopic examination) based on potential and observed risks. In controlled or dose-ranging trials, both the subjects and the health care providers who assess the subjects for safety should generally be blinded to which drug and dose of drug the subject received. Whenever possible and ethical, safety should be assessed in the entire spectrum(s) of disease severity expected to be seen in the target patient population, including normals and the critically ill. Special safety studies may be required in patients who have impairment of the organ(s) or pathway(s) involved in the distribution, metabolism or excretion for a Class 2 diagnostic radiopharmaceutical (e.g., renal, hepatic, or cardiac impairment) or in patients with impairments in the system which the agent is designed to evaluate (e.g., neurological disorders with altered receptor numbers). However, these special population studies are not mandatory for Class 1 diagnostic radiopharmaceuticals, except where appropriate for pediatric populations. The

duration of safety surveillance post-administration must be chosen with care and be defensible by scientifically valid criteria. Although immune-type phenomena are theoretically possible for any agent, Class 2 agents exhibit a higher potential risk, and may require more extensive documentation of the potential for "sensitization." Changes in manufacturing processes that alter the final drug product may require additional monitoring of patients in different phases of the drug's development.

IV. LABELING

The proposed labeling (package insert) should follow the outline provided in 21 CFR § 201.57 and should provide to physicians and other health care workers the information necessary for the safe and effective use of the drug in human patients. Factors that may affect the safety or efficacy of the drug should be identified in the package insert so that physicians may tailor the use of the drug to individual patients whenever necessary and possible as discussed below. Factors unique to diagnostic radiopharmaceuticals relate to their pharmaceutics; the intended patients; and the operation of the medical imaging equipment.

A. PHARMACEUTICS

Complete instructions for the preparation of the agent for administration should be detailed, including methods and limits for quality assurance testing when applicable. The stability of the drug (shelf-life and stability after dose preparation), the chemical stability or reactivity of the drug when mixed with other drugs prior to or during administration, and the compatibility of the drug with materials commonly found in devices which will be used in its administration (e.g., syringes, intravenous tubing, catheters, etc.) should be indicated. Additional factors such as information concerning the radioisotope (e.g., radioactive half-life), radiation dosimetry and specific activity considerations should also be included.

B. PATIENT FACTORS

Patient factors which could influence the safety and/or efficacy of the imaging procedure should be described. These could include characteristics of the target patient population (e.g., race, gender, age, height, weight, body surface area), concomitant medications and other therapies (e.g., radiation therapy, surgery, phototherapy, physical therapy), types and severity of concomitant illnesses or conditions (e.g., location, extent, and/or severity of disease), functional ability overall and of vital organs, and possibly other factors, depending on the drug and the patient population. The impact of impairment of the organ(s) or pathway(s) of the distribution, metabolism, and/or excretion of the drug should be described.

C. OPERATING FACTORS

Operating factors that pertain to the diagnostic imaging procedure should be detailed. The ranges of conditions likely to be encountered during imaging procedures should be identified and their impact on the safety and efficacy of the drug should be described. These may include the type of the diagnostic imaging instrument(s) to be used during the procedure; the time of imaging after drug administration; the kinetics of imaging relative to the pharmacodynamics of the drug and patient motion; the mode of image collection (e.g., planar vs. computed tomographic images); the frequency of image collection in dynamic studies; and the observed intra- and inter-operator variability.

V. GLOSSARY

Accuracy pertains to how faithfully the information obtained using a diagnostic radiopharmaceutical reflects reality or "truth," as measured by a gold standard test. A gold standard is an independent method of measuring the same variables being measured by the investigational drug, that is known, believed, or defined to give the "true" value of the measurement. The gold standard is taken to be the truth against which the results obtained with the investigational radiopharmaceutical are compared to determine the accuracy of the investigational radiopharmaceutical.

Precision pertains to the reproducibility of a test, including reproducibility within and across drug doses, rates of administration, routes of administration, timings of imaging post-administration, instruments, instrument operators, patients, and image interpreters, and possibly other variables. Precision is usually expressed in terms of variability, using such measures as confidence intervals and/or standard deviations; the narrower the confidence interval (or the smaller the standard deviations), the more precise the test.

Sensitivity is the fraction of cases with disease or biochemistry for which the test gives a positive result; it is also called the true positive rate. It can also be thought of as the probability of a positive test result in a patient who has the disease.

Specificity is the true negative rate, or the fraction of cases without disease or biochemistry for which the test gives a negative result. It can be thought of as the probability of a negative test result in a patient who does not have the disease.

Positive Predictive Value is the proportion of cases with positive test results that truly have disease. It can be thought of as indicating the probability of disease, given a positive test result.

Negative Predictive Value is the proportion of cases with negative test results that truly do not have disease. It can be thought of as indicating the probability that a patient does not have disease, given a negative test result.

Overall Accuracy is simply the fraction of cases in which the test result is correct, i.e., concordant with the gold standard, and can range from 0 to 1, although it is often expressed as a percentage (from 0% to 100%).