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Design, Development, Evaluation, and Approval
of New Radiopharmaceuticals

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DESIGN, DEVELOPMENT, EVALUATION, AND APPROVAL
OF
NEW RADIOPHARMACEUTICALS

STATEMENT OF OBJECTIVE

The goal of this correspondence lesson is to review the complete drug approval process, from discovery to approval, as it is currently in place. Specifically, the purpose of this continuing education lesson is to increase the participant's knowledge of the design, development, evaluation and approval of new radiopharmaceuticals.

Upon successful completion of this material, the reader should be able to:

1. define a drug substance and a drug product
2. describe the steps of drug development and evaluation.
3. identify the steps required for regulatory approval
4. describe the three phases of human clinical trials
5. define ADME.
6. find Food and Drug Administration (FDA) regulatory guidance documents on the Internet
7. list the sections of an Investigational New Drug (IND) application
8. identify the radioactive drug substance properties required for an IND
9. list some of the key provisions of the FDA Modernization Act of 1997

COURSE OUTLINE

I. RADIOPHARMACEUTICALS: A BRIEF REFRESHER

II. DESIGN OF NEW RADIOPHARMA-CEUTICALS: FINDING A LEAD COMPOUND

III. DEVELOPMENT OF NEW RADIO-PHARMACEUTICALS: OPTIMIZING THE PRODUCT

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V. APPROVAL OF NEW RADIOPHARMA-CEUTICALS

DESIGN, DEVELOPMENT, EVALUATION, AND APPROVAL OF NEW RADIOPHARMACEUTICALS

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INTRODUCTION

The term "drug" means *(a) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (c) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (d) articles intended for use as a component of any articles specified in clause (a), (b), or (c).* Radiopharmaceuticals, like other drugs, must go through a very specific process to be approved for human use. This approval process for radiopharmaceuticals may change due to the FDA's mandate (Title I, Subtitle A of the FDA Modernization Act of 1997, S. 830) to streamline this procedure.

RADIOPHARMACEUTICALS: A BRIEF REFRESHER

A radiopharmaceutical is a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. This is the single most important characteristic that separates radiopharmaceuticals from conventional pharmaceuticals.

The drug discovery process begins with studies of the actions of the radiopharmaceutical. These actions can be used to predict which chemical species will be likely to have a beneficial effect. Traditionally, fortuity has played a significant role in radiopharmaceutical drug discovery. However, the process of drug discovery is generally guided by prior art, i.e., prior developments (scientific literature, patents, company trade secrets). Data linking chemical structure and biological activity (structure

activity relationships, SAR) are often available or obtainable. Sophisticated computer modeling programs can help guide one to a class of compounds or even an optimized chemical compound. Any such studies must begin with a consideration of the aim of the drug discovery process.

Often, there is a medical area in which there is an unmet need. This can give rise to a complete clinical description of the desired drug. A primary consideration is whether the drug is to be used for diagnosis or therapy. The choice of radionuclides is thus subdivided. Diagnostic radiopharmaceuticals can be further subdivided into single photon emitters and positron emitters. Single photon emitters will be discussed first.

Single photon emitting diagnostic radiopharmaceuticals are ideally radiolabeled with a gamma emitting radionuclide that has a physical half-life of a few hours and a monoenergetic photon in the range of 50 - 300 keV. The physical half-life should be short enough to allow rapid collection of images and long enough to permit use throughout the clinical day. A shorter half-life will also minimize radiation exposure to the patient. Radionuclide generator systems can help reconcile these contradictory goals. The photons emitted during nuclear decay should be compatible with existing nuclear medicine camera technology. Most nuclear medicine cameras are based on detectors made of sodium iodide crystals. These crystal detectors work optimally with photons of no more than a few hundred keV energy. The emitted photon needs to have a minimum energy that allows escape from the body and detection by the nuclear medicine camera. With very

few exceptions, new diagnostic radiopharmaceuticals are based on the radionuclide technetium-99m (Tc-99m). Characteristics of an ideal radionuclide are shown in Table 1.

Tc-99m is generally the isotope of choice because there is an existing, successful radionuclide generator system. The Molybdenum-99 (Mo-99)/Tc-99m generator delivers high yields of sterile, pure, isotonic sodium pertechnetate. Molybdenum-99 has a physical half-life of about 66 hours. Commercial Mo-99/Tc-99m generators can easily be used for a week with no loss in performance, other than decreased yields of Tc-99m due to radioactive decay of the Mo-99. This one-to-two week useful lifetime facilitates convenient manufacture and distribution. Maximum activity yield of Tc-99m occurs at about 24 hours, which allows for convenient daily clinical use. The generator is simply eluted daily with a sterile normal saline solution. The resultant sodium pertechnetate is ready for reaction with a non-radioactive radiopharmaceutical reagent kit. In addition, Tc-99m has a physical half-life of 6 hours and a monoenergetic gamma (photon) emission of 140 keV. Both of these values are compatible with routine clinical use.

Tc-99m-based radiopharmaceuticals consist of two parts: the Mo-99/Tc-99m generator and the non-radioactive ("cold") reagent kit. Both parts are necessary for generation of the Tc-99m labeled radiopharmaceutical. Both require full regulatory approval, as discussed below. In many cases, these two parts will be obtained by the clinical user from different manufacturers.

Table 1. Characteristics of an Ideal Diagnostic Radionuclide

Characteristic	Optimal Value(s)	Common Commercial Example(s)
Emission	Monoenergetic Photon	Tc-99m, I-123
Photon Energy	50 B 300 keV (compatible with traditional NaI(Tl) crystal technology	Tc-99m, I-123, Tl-201
Half-life	Greater than 24 hours for shipping; 2 B 6 hours for biological localization and imaging	Mo-99/Tc-99m generator system
Production	High yield; reactor: thermal neutron capture; or accelerator: low energy [(p,n) or (p,2n)] proton bombardment	Mo-99/Tc-99m, I-123, F-18
Target Material	Inexpensive (abundant stable isotope)	Mo-99/Tc-99m, I-123 [I-127 (p,5n)], Tl-201
Recovery from Target	Simple physical and chemical manipulations that can be performed remotely (e.g. remote manipulators or robotics)	I-123 [Xe-124(p,2n) or I-127(p,5n)], Tl-201, Mo-99/Tc-99m, F-18
Chemistry	Can quickly and quantitatively be incorporated into many chemical species of pharmaceutical interest	I-123, F-18, Tc-99m

The technetium-based radiopharmaceutical reagent kit contains the drug precursor (or ligand) that will react with pertechnetate to form the radioactive drug substance, a Tc-99m complex. Discovery of the ligand constitutes the first, and the most difficult, phase of drug development. In starting this process, a primary or "lead" compound must be identified. Generation of a lead compound can occur in many ways. Sometimes a chemical species is identified in-house by the research and development (R&D) department of a radiopharmaceutical company. Lead compounds are often found by academic researchers. License and patent agreements between the academic researchers and a radiopharmaceutical company allow development to proceed.

Despite its excellent physical properties, Tc-99m can be a difficult metallic element with which to work, from a radiochemical point of view. Technetium is a transition metal with multiple valence (oxidation) states ranging from the +7 state of pertechnetate to -1. The valence state to be accessed depends on the nature of the ligand to be complexed. As a result of the interest of the nuclear medicine community, spectacular gains have been made in recent years in the understanding of technetium chemistry.

The non-radioactive reagent kit may contain various other chemicals besides the ligand (or pharmaceutically-active chemical component). The most notable of these is a reducing agent. The reducing agent is used to lower the oxidation state of the technetium from +7 in pertechnetate. At the lower oxidation state, reaction between the technetium and the ligand (drug precursor) can take place. Kits may also contain anti-oxidants, anti-microbials, inert gases (in the headspace of the drug container). bulking agents, buffers, pH adjusters (acids and bases), and transfer ligands.

In technetium-based cold kits, stannous chloride is the most commonly used reducing agent. As the technetium is reduced from oxidation state +7 to some lower value, stannous tin (+2 oxidation state) is oxidized to stannic tin (+4). To prevent oxidation of the stannous ions before their intended use, anti-oxidants and inert gases may be added to the kit vial. Oxygen from air leaking into the cold kit container can oxidize the stannous tin before use.

Anti-microbial agents are used to prevent the growth of bacteria both before and after the addition of the sterile normal saline containing the Tc-99m. Many technetium cold kits are lyophilized (freeze dried). Bulking agents are chemically inert substances that aid in the lyophilization process. Transfer ligands are used when a multiple step chemical reaction is required to form the final technetium complex. Transfer ligands are designed to "chemically hold" the technetium while slower chemical reactions take place. The reduction of technetium by stannous tin can be a fast reaction when compared to the steps necessary to present the ligand in the proper chemical form for reaction

with technetium.

Some technetium kits require more than one vial. In such cases, transfer and processing or compounding steps are necessary to produce the radiopharmaceutical. All these containers, with their ingredients, are part of the radiopharmaceutical preparation.

Positron emitting nuclides give rise to a subcategory of diagnostic agents. Imaging of such substances is known as positron emission tomography (PET) and the radiopharmaceuticals are called PET drugs. Emission of a positron (a positive electron) from the decaying nucleus eventually results in the creation of two 511 keV photons emitted 180 degrees from one another. These photons are more energetic than photons commonly used with conventional diagnostic radiopharmaceuticals. Thus, positron cameras often use detectors with better capture efficiencies than sodium iodide.

The drug discovery process for PET is similar to that for single photon diagnostic radiopharmaceuticals. The radionuclides suitable for PET use are different and again place rigid constraints (largely due to physical half-life) on what drugs can be developed for human use. A "workhorse" radioactive generator equivalent to Mo-99/Tc-99m has not been identified for PET. The most widely used PET radionuclide is fluorine-18, which has a half-life of about 110 minutes. In this case, the physical half-life confines shipment times to a few hours. The short half-life changes the areas of emphasis in radiopharmaceutical production and use processes. The product is delivered to the customer in a ready to use ("hot") form. However, the same design, development, evaluation, and approval considerations apply.

Therapeutic radiopharmaceuticals are an area of intense commercial development. These drugs, radionuclides which decay with the loss of a beta (electron from the decaying nucleus) or an alpha (helium-4) particle, are generally chosen. These relatively heavy particles significantly interact with biological tissue resulting in a substantial transfer of energy to tissue close to the location of their creation. All the precepts of drug discovery apply. Radiotherapeutics are available as "hot" agents and also in kit form. In contrast to many PET agents, decay (timing), while an important factor, is not the critical parameter. In general, radiation dose to non-target tissues becomes the number one confounding factor for use of these drugs. Radiopharmacology and radiopharmacokinetics studies (discussed later) become the focus of pre-clinical and clinical studies, as opposed to the case for non-therapeutic radiopharmaceuticals.

Three important concepts in the development of a new pharmaceutical are "drug substance," "final intermediate," and "drug product." The drug substance is defined by the FDA as "the material that is intended to furnish pharmacological activity or other direct effect in

the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body." In the case of technetium-based kits, the drug substance generally is formed "*in situ*" upon addition of the eluate from a Mo-99/Tc-99m generator. The ligand in the kit that complexes with the Tc-99m is referred to as the "final intermediate." The final intermediate of drug manufacturing is thus the last compound synthesized before the reaction that produces the drug substance. In contrast, the drug product comprises the drug substance and everything else that is administered to the patient. For Tc-99m labeled radiopharmaceuticals the drug product includes the entire contents of the kit/eluent mixture: normal saline, buffers, reducing agent, anti-oxidants, transfer ligands, bulking agents, etcetera.

DESIGN OF NEW RADIOPHARMACEUTICALS: FINDING A LEAD COMPOUND

The first step in the design of a new radiopharmaceutical is the research and development process which involves identifying a lead compound. Some companies focus on developing drugs for use in broad disease categories such as cancer. Such drugs are intended to be used against a variety of disease subtypes. Other companies may search to target a specific disease, for example a renal function agent. Additionally, some drugs are discovered serendipitously. Once a category of interest is selected, many critical decisions are made to bring that drug product to market.

A lead compound is selected by either random screening, combinatorial chemistry or targeted synthesis. While the odds for success with random screening each compound are low, a researcher who perseveres can be successful with the random screening technique. The random screening technique uses an existing library of chemical agents. Combinatorial chemistry and screening is more complex but improves the odds of success. This process involves using one compound as a base, then randomly adding molecular segments of other agents to enhance the base compound's activity and disease-identifying (or fighting) potential. Targeted synthesis focuses on a particular step in a disease process as a target for drug intervention. Targeted synthesis also requires the screening of hundreds of compounds and an extensive amount of research initially to understand a particular disease process. The most inexpensive method for identifying compounds worthy of the drug development process is drug modeling. Researchers begin with a compound that they know has some utility but requires changes in the chemical structure to enhance its potential. Much of drug modeling is performed by sophisticated computer programs.

Once a lead compound has been identified, a battery of tests are conducted to determine if the compound works in animals and whether there are any potential side effects and/or serious toxicities. Once an agent's [a]potency, [b]absorption (bioavailability), distribution, specificity, and other properties have been determined, it is possible to assess whether the drug is a viable candidate for development. If the results are promising, chemical synthesis scale-up can begin. Even for radiopharmaceuticals, such scale-up is necessary since R&D quantities of material will not be sufficient for production. It is important to determine if efficient methods of preparation of the necessary drug precursors and components are available. Costs associated with drug preparation are an important factor to be considered in the decision to proceed to the next level of drug development. Thus, at this stage, there are many potential obstacles in the manufacturing process. Large quantities of the drug product will be required while maintaining a high level of purity with little risk to the environment or employees. Typically, a radiopharmaceutical will require kilogram quantities of drug product. Traditional pharmaceuticals usually require hundreds of kilograms. The compound of interest will need to be formulated into a form which is easy for patient administration and chemically stable during a useful shelf life of the product. Since radiopharmaceuticals are usually injected, the drug needs to be well-tolerated and non-irritating to the veins. This generally implies an isotonic or nearly isotonic formulation.

[a, b] *The considerations of potency and absorption are often irrelevant with regard to design of radiopharmaceuticals.*

DEVELOPMENT OF NEW RADIOPHARMACEUTICALS: OPTIMIZING THE PRODUCT

Generally, development of analogs chemically-related to the first candidate compound proceeds simultaneously with testing of this lead compound. A well-defined set of objectives is important at this stage. The company needs to know if any given candidate is "good enough." Traditionally, a company's knowledge and chemical intuition has played a large part in determining what analogs are synthesized and tested. Computer-based chemical modeling schemes are being used with increasing frequency as the sophistication and usefulness of such techniques increase. In many cases, all analogs that are easy to synthesize are prepared. The idea is that intuition and modeling are imperfect; sometimes brute force (persistance) works just as well.

Formulation studies now become a critical step. For cold kits with expected shelf lives of many months to years, the exact choice of ingredients can be crucial. One usually has many man-years of retrospective data to draw on in the formulation of a drug. It is important to be fully

cognizant of both the scientific literature and the patent literature before beginning a formulation process. Many "chemical use" patents limit the ingredients and combination of ingredients that one can use commercially with a new product. Most often an extensive matrix of formulations is identified and prepared by the R&D staff. Each formulation is then put through a standard battery of fitness-for-use tests. These tests are biological, chemical and physical in nature. Since time is always of the essence in drug development, the tests are often abbreviated versions of the tests required to generate data for the FDA submissions.

Even prior to formulation development, testing can begin with the newly identified lead compound. A unique and vital feature of radiopharmaceuticals is the requirement for radiolabeling. If the product is to be delivered to the customer as a radioactive (hot), ready-to-use preparation, labeling can be somewhat technically difficult. However, if the drug is sold as a cold kit, radiolabeling must be quick, easy, and quantitative. Radiolabeling studies are some of the first to be conducted. In the drug design phase (previous section) a lead compound can be synthesized utilizing low yield, crude radiolabeling techniques. During the drug development phase, these radiolabeling procedures must be "fine-tuned" and made efficient.

Stability testing is initiated immediately, even before the best agent has been identified. At this R&D stage, a close analog of the final drug precursor can sometimes be used for obtaining immediate answers. Drug formulations involve many different chemicals and basic chemical compatibility issues need to be identified as early as possible. Accelerated stability testing involves storage at high temperature and/or high humidity. For Tc-99m-based products (or any radionuclide generator-based drug), both the cold kit and the final radiolabeled drug must be tested. Any data later officially submitted to the FDA must use the actual active ingredient.

Drug identity, formulation, stability and radiolabeling studies proceed simultaneously. Each drives the other. The challenge to the R&D staff is to meet product specification goals in several diverse areas. Once a promising agent has satisfied laboratory criteria, the next step is to progress into the biological arena. However, synthesis and biological testing will continue to progress simultaneously until a suitable lead candidate is identified. At this stage, selection of one or more animal models is critical. Although accurate animal models have been determined for many disease conditions, even established biological methods may be misleading if a new chemical class of agents are being tested. The history of drug development is replete with stories of extensive animal testing of agents yielding positive results that did not translate to human studies. As an example Tc-99m DMPE (bis(1,2-

dimethylphosphino)ethane), was successfully tested in several animals species before failing clinical trials in humans.

Pharmacology is primarily concerned with drug effects and distribution. These can include alterations in the normal function of an existing biological process. However, diagnostic radiopharmaceuticals are designed to measure physiological parameters or biological processes based on the in vivo distribution of the radioactivity. Thus, any pharmacological or physiological effects induced by a diagnostic radiopharmaceutical would be considered side effects. In general, most diagnostic radiopharmaceuticals have a high specific activity (measured as Ci/mmol) at the normal dosage range (1 to 30 mCi). In these cases, the net amount of chemical being introduced into the blood circulation is extremely small (in the millimole to picomole range).

Radiopharmaceuticals are usually injected intravenously. Since they are generally not administered orally, one does not have to contend with passage of the drug through the membrane lining of the gastrointestinal tract. This limits the amount of bioavailability testing that is needed. It is also beneficial for radiopharmaceuticals since only a few of them are structurally suitable for transport across gastrointestinal membranes.

Absorbed dose (dosimetry) is a consideration unique to radiopharmaceuticals. Absorbed-dose calculations and measurements are required for the evaluation of the risk involved with any radiopharmaceutical. This includes diagnostic, therapeutic, or any noninvasive physiological or metabolic study. The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine, among others, has published extensively on the MIRD schema. Briefly, internal dose estimates are made by determining the radiation absorbed in various target tissues from a number of source organs in the body.

The amount and type of biodistribution or radiopharmacology performed in order to calculate dosimetry depends on the exact nature of the radiopharmaceutical. For example, agents binding to receptors in the central nervous system (CNS, brain) mandate more detailed tissue distribution studies than those drugs intended to measure blood flow. Extensive in vitro competitive cell binding studies are required for neuroreceptor agents. Detailed radiopharmacokinetics of the CNS with intricate regional brain dissection studies would also be vital. Preliminary versions of these studies would be performed as crucial product testing during the drug design phase (previous section) for receptor-based radiopharmaceuticals. Studies might include autoradiography and competitive binding inhibition.

The next important step in drug development is determining the relative toxicity of the new chemical

compound. Toxicity studies in animals continue to serve as a basis for many regulatory actions. The biological complexity of higher animals makes extrapolation of data somewhat uncertain. Most new drugs are administered to specially bred animals in carefully controlled environments. Such tests are important in determining which drugs are most likely to be safe when given to man.

Acute toxicity studies are an important component of in vivo drug testing. Traditionally, acute toxicity studies have been directed toward computation of a single dose which will be lethal to 50% of the animals (LD_{50}). In recent years, other more sophisticated measures of toxicity have been developed. These newer methods do not rely on a single point (LD_{50}) to characterize the degree of toxic reaction. Acute toxicity studies should also be designed to identify any drug-induced lesion. It is recommended that three animal species (one a non-rodent) be used in the tests. The animals in the study protocol should be observed for at least a week following dosing as delayed deaths can occur. Necropsies of all animals which die after dosing, or are sacrificed at the end of the study, are necessary. For radiopharmaceuticals, it may be difficult to obtain the necessary amounts of the drug substance for injection at a lethal level. Especially for Tc-99m-based diagnostic agents, preparation of sufficient Tc-99m complex may be problematic. In such cases, it is recommended that the sponsor contact the FDA for guidance. Dosing at a large multiple of the expected clinical dose (e.g., a factor of 1000 or more) may be sufficient to establish an acceptable lower toxicity threshold.

Selection of doses for multidose subacute toxicity studies needs to be determined on a case-by-case basis. One should not simply calculate ratios to the proposed clinical dose or to the LD_{50}. Additionally, in all toxicity studies, the route of drug administration to animals should be the same as that proposed in clinical studies.

Since diagnostic radiopharmaceuticals are generally administered in small mass amounts, chances of an adverse reaction due to interaction with another drug is low. However, one needs to be aware of the potential for adverse or abnormal drug reactions, especially in chemotherapeutic patients. For example, binding profiles of receptor agents may be affected by therapeutic drugs targeted at the same receptor.

In designing subacute (chronic) toxicity studies, one should use at least one rodent and one nonrodent species. Each study needs to include enough animals to allow an accurate estimation of the incidence and frequency of toxic effects. Many radiopharmaceutical manufacturers prefer to contract out subacute toxicity studies since the protocols are rigorous and specialized. A typical subacute study may include 10 to 20 animals per group per sex. Each study should include a control group. For diagnostic radiopharmaceuticals, the subacute toxicity studies should

be carried out for at least two weeks and perhaps four to six weeks. It is presumed that diagnostics will not be used chronically in the clinic. Therapeutic radiopharmaceuticals may be administered many times over a several month period and thus longer subacute toxicology studies may be mandated. If the drug is to be given over a three-month period, up to a 12-month subacute study may be appropriate. Allergic reactions may develop after administration of multiple doses of biologics such as radiolabeled monoclonal antibodies.

Several observations and determinations need to be made during the course of the subacute study. Gross clinical observations may include appearance, behavior, salivation, diarrhea, food and water consumption, and weight. Clinical chemistry tests to be performed will depend on the exact nature of the radiopharmaceutical. Appropriate tests often will include measures of metabolism (blood glucose), liver function (SGPT), kidney function (BUN), and possibly measures of electrolytes, hormones, etcetera.

Biopsy can be useful for monitoring the histological status of certain tissues. However, necropsy is essential. All major tissues of all animals which die or are sacrificed should be examined. Histopathology should be routinely performed. All major tissues should be fixed and sectioned. This includes the heart, spleen, lymph nodes, lung, pituitary, kidney, liver, intestines, prostate, uterus, ovary, thyroid, bone and brain. Signs of aging and abnormal life span should be noted.

Reproduction and teratology studies may be required. A drug's potential effect on the reproductive process must be considered. As before, the chance of a single-use diagnostic agent causing such effects is very low. Nevertheless, it is recommended that a drug developer contact the FDA on a case-by-case basis to determine the requirement for such studies.

Pharmacokinetic studies should play a role in every stage of drug development and evaluation. Radiopharmacology yields vital information about the disposition of the drug and its metabolites. Conventional measures of drug metabolism are also needed. Radiopharmacokinetics is concerned with absorption, distribution, metabolism and excretion (ADME) of the radioactive drug. A prerequisite to effective pharmacokinetic studies is the development of analytical methodology to assay the parent radiopharmaceutical and the major metabolites in biological fluids. Radiotracers lend themselves well to this type of study. One should meld radiochemistry techniques with conventional methods of analysis such as high pressure liquid chromatography (HPLC), gas chromatography (GC), and electrophoresis to obtain optimum analytical protocols. Determination of pharmacokinetics with radiolabeled tracers can yield exquisitely sensitive results. Biological

pathways can be more accurately determined since the system under study is not saturated with the test agent. In recent years, traditional pharmaceutical companies have increasingly employed the method of radiolabeling their drugs in an effort to improve ADME studies for their agents.

Preclinical studies should include information on the metabolic fate of the radiopharmaceutical. One must be guided by one's knowledge of chemistry and biochemistry to ascertain possible metabolites. Synthesis and characterization of these species will be necessary to determine if metabolism is indeed taking place. It is important to consider seriously the possibility that metabolites themselves may be biologically active. It is also important to recognize that drug metabolism studies in humans often provide results which are significantly different from those obtained in animals.

We now briefly consider sources of regulatory information regarding the incorporation of new radiopharmaceutical use measures to facilitate drug development. As radiopharmaceutical development progresses from clinical Phase 1 to Phase 2 to Phase 3 (defined later in this lesson), the amount of safety information that should be provided to the FDA increases. More information about the various components of the drug substance and drug product portion of the application is required. The FDA has developed a series of guidances that describe how applicants may conduct studies. Persons with access to the Internet may obtain the guidance documents using the World Wide Web (WWW). For WWW access, connect to the Center for Drug Evaluation and Research (CDER) at http://www.fda.cder/guidance/index.htm.

Meetings with the FDA can improve the filing of applications pertinent to the drug approval process.. The CDER Manual of Policies and Procedures lists types of meetings and how they can help provide assistance to the drug manufacturer. Formal meetings provide clarity and resolve issues related to the drug development and review processes, compliance actions, and policy development. The FDA favors a transparent approach to scheduling and conducting formal meetings (face-to-face, teleconference, and videoconference). Requests for a formal meeting with a FDA (CDER) division should be made in writing. The written request should provide (1) a statement of the purpose of the meeting, (2) a list of the specific objectives of the meeting, (3) a proposed agenda, (4) a list of company attendees, (5) a list of requested FDA participants, and (6) timing of mailing of supporting documentation. Information and/or supporting documentation necessary for a productive meeting does not need to be submitted before a meeting will be scheduled. If the meeting is granted by the FDA, details may be confirmed by telephone. Generally such meetings will lead to quicker approvals.

Following a multi-year trend, it is expected that the Investigational New Drug (IND) portion of drug development is going to continue to be compressed. However, each drug product must be considered individually regarding the major safety concerns. Guidances are now being developed at the FDA as to what information should be submitted to the FDA during the various phases of the IND application. Regulations for the conduct of the IND studies are listed in the Code of Federal Regulations, Chapter 21, Part 312 (21 CFR 312). Additionally, regulations on the protection of human subjects in clinical investigations regarding informed consent and institutional review board (IRB) review and approval are set forth in 21 CFR Part 50 and 21 CFR Part 56, respectively. The IRB is legally an arm of the FDA. The IRB thus constitutes many applicants' first contact with the federal regulatory process.

EVALUATION OF NEW RADIO-PHARMACEUTICALS: THE IND APPLICATION

The approval process begins with the submission of an Investigational New Drug Application (IND) [Form FDA-1571]. The FDA has 30 days following receipt of an IND to decide if it is reasonably safe for the drug sponsor(s) to initiate the proposed clinical study. Assuming that the study is initiated, the study progresses though three phases, each involving a larger and larger subject base. Changes to any part of the IND must be reported to the FDA as amendments to the application. These amendments are reviewed by FDA personnel as are the yearly progress reports for each IND. To obtain evidence needed to show a drug is safe and effective, the applicant must perform studies in animals (preclinical studies) and in humans (clinical studies). If the drug looks promising in preclinical studies, human clinical studies are proposed in the IND.

The IND must contain sufficient information to show it is reasonably safe to begin human testing. An IND for a new molecular entity will ordinarily include, in addition to other information, the results of preclinical studies, the protocols for the planned human tests, and information on the drug's composition, source, and method of manufacture. Drug testing in humans proceeds through three phases, Phase 1, 2, and 3. Phase 1 includes the initial introduction of an investigational drug into humans and consists of short-term studies in a small number of healthy subjects, or patients with the target disease, to determine the metabolism and basic pharmacologic and toxicologic properties of the drug. Phase 2 consists of larger, more detailed studies, usually including the first controlled clinical studies intended to assess the effectiveness of the drug and determine the common

short-term side effects and risks of the drug. Phase 1 and 2 investigations serve to ensure consistency of multiple batches used in clinical trials and justify drug product specifications.

The data identified in the Phase 3/pivotal studies section need not be submitted prior to the initiation of the pivotal study(ies). As clinical development of the drug product proceeds, sponsors should discuss with the FDA what recommended manufacturing data are needed to support the safe use of the drug in all investigational phases. The FDA has encouraged sponsors to meet with the team prior to the initiation of pivotal clinical trials to discuss issues and protocols, which might impact the approvability of the New Drug Application (NDA). During Phase 3/pivotal trials, the sponsor should provide updates on the information specified for Phases 1 and 2. Sponsors may request a rolling Chemistry, Manufacturing and Controls (CMC)·submission of material during Phase 3 which will be essentially identical to what will be filed in the NDA. The FDA/sponsor meetings and the pre-NDA filing for a rolling CMC submission should improve the efficiency of the review process. At the Phase 3/pivotal study, the drug substance and drug product should be fully described by the physical, chemical, and biological characteristics. In addition to the information provided during Phases 1 and 2, updates of the acceptance criteria and analytical procedures for assessing the quality of starting material(s) should be provided. An updated detailed flow diagram should also be provided. The flow chart should contain the chemical structure and configuration including stereochemical information of the starting materials, intermediates and significant side products. A detailed list of all the tests performed should be provided. A general description of the procedure should be provided followed by the specific United States Pharmacopeia (USP) or Test Procedure Number, as appropriate. Impurities should be identified, qualified, and quantified as appropriate. Suitable limits based on manufacturing experience should be established. Suitable microbial limits should be established and updates reported for non-sterile products. The container/closure system used to transport and /or inventory the bulk drug substance should be described in detail. Stress studies should be performed to demonstrate the inherent stability of the drug substance and drug product. potential degradation pathways and the capability and suitability of the proposed analytical procedure. The stability protocol submitted should include a detailed description of the drug substance and drug product under investigation, packaging, a list of the tests, procedures, sampling time points for each test and the expected duration of the accelerated and long term testing program.

With the FDA's recent successes in meeting the Prescription Drug User Fee Act of 1992 (PDUFA) review action performance goals, and the resulting significant declines in mean and median time from submission of a marketing application to approval for marketing, attention has turned to increasing the efficiency of other components of the drug development process without sacrificing the long standing safety and efficacy standard. One part of the IND regulation is the initial testing of drug in humans (i.e. Phase 1 trials). The November 1995 *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology -derived Products*[1], clarifies the requirement for data and data presentation in 21 CFR 312.22 and 312.23 related to the initial entry into human studies of an investigational drug (in the United States). Under current regulations, any use in the United States of a drug product not previously authorized for marketing in the United States first requires submission of an IND to the FDA. This provision holds whether the work is sponsored by a pharmaceutical manufacturer or an individual such as a licensed physician. Regulations in 21 CFR 312.22 and 312.23 contain the general principles underlying the IND submission. The general requirements for an IND's content and format are shown in Table 2.

Present FDA guidances allow a great deal of flexibility in the amount and depth of various data to be submitted in an IND depending in large part on the phase of the investigation and the specific human testing being proposed. Many of these guidances have reduced the amount of information needed for submission. The most significant clarifications within these guidances are (1) the explicit willingness of the FDA to accept an integrated summary report of toxicology finding [21 CFR 312.23(a)(8)(ii)(a)] based upon the unaudited draft toxicologic reports of completed animal studies as initial support for human studies, and (2) specific manufacturing data appropriate for Phase I investigation.

The Introductory Statement and General Investigation Plan [21 CFR 312.23(a)(3)] is intended to place the developmental plan for the drug into perspective and to help FDA anticipate sponsor needs. Often a sponsor in the first human studies is simply attempting to determine early pharmacokinetic and perhaps early pharmaco-dynamic properties of the drug. Detailed developmental plans are contingent on the outcomes of such studies. In that case, sponsors should simply state such in this section and not attempt to develop and write detailed developmental plans that will, in all likelihood, change considerably should the product proceed to further development.

Under the auspices of the International Conference on Harmonization (ICH), the "Good Clinical Practice: Guideline for the Investigator's Brochure" has been developed and published in the *Federal Register*. Sponsors

Table 2. IND Requirements.

SUBMISSION ITEM	CODE OF FEDERAL REGULATIONS REFERENCE
Cover Sheet (FDA Form -1571)	21 CFR 312.23 (a)(1)
Table of Contents	21 CFR 312.23(a)(2)
Introductory Statement and General investigational Plan	21 CFR 312.23(a)(3)
Investigators Brochure	21 CFR 312.23(a)(5)
Protocols	21 CFR 312.23(a)(6)
Chemistry, Manufacturing, and Control Information	21 CFR312.23(a)(7)
Drug Substance	21 CFR 312.23(a)(7)(iv)(a)
Drug Product	21 CFR 312.23 (a)(7)(iv)(b)
Composition, manufacture, and control of any placebo to be used in the proposed clinical trials(s)	21 CFR 312.23(a)(7)(iv)(c
Labeling	21CFR 312.23(a)(7)(iv)(d)
Categorical exclusion for or Submission of an Environmental Assessment	21CFR 312.23(a)(7)(iv)(e) see *Guidance for Industry for the Submission of Environmental Assessment for Human Drug Applications and Supplements*, November 1995.
Pharmacology and Toxicology Information	21 CFR 312.23(a)(8)
Previous Human experience with the Investigational Drug	21 CFR 312.23(a)(9)

are referred to this document for further information on recommended elements of an investigator's brochure. Sponsors are reminded that the regulations were changed in 1987 specifically to allow Phase 1 study protocols to be less detailed and more flexible than protocols for Phase 2 or 3 studies. This change recognized that these protocols are part of an early learning process and should be adaptable as information is obtained, and that the principal concern at this state of development is that the study be conducted safely.

The regulations [21 CFR 312.23(a)(6)] state that Phase 1 protocols should be directed primarily at providing (1) an outline of the investigation, (2) an estimate of the number of subjects to be included, (3) a description of the safety exclusions for the subjects, and (4) a description of the dosing plan, including duration, dose or method to be used in determining dose. Protocols should specify in detail only those elements of the study that are critical to submit safety data, such as monitoring of vital signs and blood chemistries, and toxicity-based stopping or dose adjustment rules.

It is now recognized by the FDA that modification to the method of preparation of the new drug substance and dosage form, and even changes in the dosage form itself, are likely to occur, as the investigation progresses. The emphasis in an initial Phase 1 CMC submission should, therefore, generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study. The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a

clinical hold based on the CMC section. Reasons for concern may include a product made of unknown or impure components, a product possessing chemical structures of known or high likelihood of toxicity, a product that cannot remain chemically stable throughout the testing program proposed, or a product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard.

Full descriptions of the synthesis of both the final intermediate and the drug substance must be included in the IND application. Any in-process controls, including specification and test procedures are required, even in those cases where intermediates are not isolated. Any evidence used in the structure elucidation must be included as well.

Where a short-lived radionuclide is involved, it may not be possible to fully characterize the drug substance. In this case, it is advisable to synthesize the drug substance with either a longer-lived isotope or perhaps a nonradioactive isotope. Structure determination can then be performed on this material. Specifications and test procedures should be provided for all the reagents and starting materials used in the synthesis. All the reagents require acceptance with either certificates of analysis for each lot and performance of a specific identification test or full analytical testing on each lot received from the supplier.

The four criteria generally used by the FDA to define a starting material are:

- Incorporated into the new drug substance as an important structural element
- Commercially available
- A compound whose name, chemical structure, chemical and physical characteristics and properties, and impurity profile are well-defined in the chemical literature
- Obtained by commonly known procedures

When dealing with radiopharmaceuticals, the incorporated radionuclide constitutes an additional starting material in the preparation of the drug, having met all the criteria above. Additional information is also required by the FDA in the IND submission for the radioactive drug substance, since it contains a radionuclide. Thus, the presence of a radionuclide adds specification requirements beyond those necessary in conventional pharmaceuticals for the starting materials, drug substance, and drug product. These additional requirements for radioactive drug substances are stated below.

- The half-life of the radionuclide
- The physical decay scheme for the radionuclide, including the radionuclidic half-lives, principal particle and gamma emissions (with energies and relative abundances)
- A description of the radiolabeling used in the drug substance (specific, uniform, etc.)
- A discussion of potential radionuclidic, radiochemical, and chemical contaminants and their sources
- The specific activity and the maximum theoretical specific activity for the radioactive compound
- The radioactive concentration (e.g., mCi/mL) of any material containing the radionuclide
- The isotopic composition and purity
- Description of non-radioactive carrier added, if any

The radionuclide is usually produced in an accelerator or reactor. In such cases, a detailed discussion of the production and separation of the nuclide should be included in the synthesis section of the application. The pertinent nuclear reactions should be included. Whenever appropriate the target material needs to be described fully. This would include source, composition, preparation, method of irradiation, and processing.

In the case of radionuclide generator systems such as Mo-99/Tc-99m, the method of preparation of the generator, a complete description of the generator components, the source and method of preparation of the parent nuclide, information on the eluate, and a complete description of all internal and external components should be included in the application. The manufacturing process for the generator needs to be completely discussed.

If one is devising a cold kit based on an existing generator product, it is sufficient to simply reference the generator's Drug Master File (DMF). If the DMF is deficient in its description

of the apparatus, the DMF holder will be contacted by the FDA for additional information regarding the generator.

Similar information is required by the FDA for the drug product. Any radioactive component of the drug product should be listed in the composition statement. The description should include the total activity at a specified time, the radionuclidic, radiochemical, and chemical purity, and impurity limits. If the product is a cold kit that will be reconstituted with a radioactive species prior to use, two compositions are required. One will be for the cold kit and one will be for the reconstituted product. For those products containing a stannous salt as a reducing agent, the composition statement should list the total amount of material including the degree of hydration. The labeling should include the maximum combined stannous and stannic content and the minimum stannous content.

The manufacturer of the drug product needs to be listed as well as a complete description of all procedures provided, including any in-process controls. The relationship between the time of manufacture, time of radioassay, time of earliest user receipt, time of radiocalibration, and time of expiration should be included. If the radionuclide is short-lived, these manufacturing times should be related to the end of bombardment. The total radioactivity in the container and the radioconcentration should be tabulated at these various reference times.

Tests unique to radiopharmaceuticals include the following:

- Radionuclidic identify
- Radionuclidic purity and impurity limits
- Radiochemical purity and impurity limits
- Radiobiological distribution
- Carrier (non-radioactive) content

The radionuclidic identity test needs to be specific for the radionuclide of interest. The radionuclidic purity should be specified at various critical times. These may include the time of manufacture, the time of calibration, and the time of expiration. The level of radionuclidic impurities should be discussed in the same manner. Limits should be set for each individual radionuclidic impurity. The same comments apply to radiochemical purity.

An in vivo biological test should be included to demonstrate that the radiopharmaceutical is suitable for its intended use. The specifications should ensure that a sufficient amount of the product will be found in the target organ (or tissue). It is necessary that the data provide correlation to human biodistribution. Although this test is no longer re-quired as an ongoing part of drug monitoring, it needs to be done to prove that material passing all the chemical tests will behave appropriately in the body.

During Phase 2 additional information on the molecular complexity should be provided to the FDA. Tables 3 and 4 indicate how the FDA evaluates the phase 1 studies for chemistry, manufacturing and controls and what additional information is needed as the Phase 2 studies begin.

Table 3. Phase 1 and Phase 2 Requirements For the Drug Substance

Property	Phase 1 Requirements	Phase 2 Requirements
Description	A brief description of the physical, chemical, and biological characteristics of the drug substance.	Same
Characterization and Proof of Structure	Some supporting evidence to elucidate and characterize the structure should be provided. It is generally understood that the amount of information may be limited based on the early stage of development. These data should be summarized. Spectra should be available upon request.	Same
Manufacturer	The full street address of the manufacturer of the clinical trial drug substance should be stated.	Same
Starting material	The starting material should meet the definition described in the *FDA's Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*. The structure of the starting material(s) should be provided. The source of, methods and test results for the starting material should be available upon request.	Same
Reagents, Solvents, and Auxiliary Materials	At this stage of development, the reagents, solvents and auxiliary materials only need to be identified in the description of the synthesis (section 3.4) of the application. Sources of raw material derived from animals must be stated.	Same
Flow chart	A detailed flow diagram should be provided that contains the following information: chemical structure, including stereochemical configuration, if applicable intermediates and significant side products. The solvent catalyst and reagent, fermenters, columns and other equipment/reagents used for biotech or natural products.	Same

Manufacturing Process	A brief description of the synthetic or manufacturing process should be provided.	Same
Reprocessing	Reprocessing procedures and controls need not be described in phase 1.	Describe reprocessing
In-process Controls	Need not be defined	Same
Reprocess Controls	Need not be described.	Same
Reference Standard	Preparation not required in phase 1 studies	By phase 2 the reference standard should be identified (e.g., batch number).
Reference Standard Qualification	Reference standard description and qualification is not required in the submission. A working standard of known purity is suggested. Test results should be reported when available.	In phase 2 studies, additional chemical and stereo specific tests should be reported, if applicable.
Analytical Tests and Specifications	The tests performed should be indicated (e.g. description, identity, assay, levels of detection). Methods: A brief description of the analytical methods used should be submitted. Acceptance Criteria: Acceptable limits should be provided.	In phase 2 studies, the analytical methods used to perform the test and support the acceptance criteria should be indicated (e.g., HPLC). The complete description of the method and supporting validation data should be available upon request.
Purity/Impurity Profile	Data should be provided.	Same
Microbiology	Microbial limits should be considered, when appropriate.	Same
Batch Results	Test results, analytical data (e.g. IR spectrum, HPLC, chromatogram) and certificate of analysis of clinical trials material should be provided.	Same
Container/Closure system	A description of the container /closure system need not be included unless an unusual packaging system is used.	In phase 2, a brief description of the container/closure system should be provided.
Stress Stability Studies	Are not required in phase 1 studies	In phase 2 the stress testing should be conducted.
Stability Studies and Protocol	A brief description of the study and the analytical methods used to monitor the stability of the drug substance should be provided.	In phase 2 the stability protocol including a list of the tests, sampling time points for each of the tests and the expected duration of the stability program should be submitted.
Stability Data	Preliminary tabulated data based on representative material may be provided and the submitted data should be analyzed.	Same

Table 4. Phase 1 and Phase 2 Requirements For the Drug Product

Property	Phase 1 Requirements	Phase 2 Requirements
Component/composition	A table listing all components, which may include reasonable alternatives for inactive components, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear, but which are in the manufacturing process, should be provided.	By phase 2 a quantitative composition per unit of use should be provided (e.g., ug/mL).
Batch formula	In phase 1 the batch formula is not required	In phase 2, a batch formula should be provided.
Active Ingredients	Acceptance testing of the drug substance by the manufacturer of the drug product should be described if the drug product is manufactured at a different site or by a different manufacturer.	Same
Inactive Ingredients Compendial	The quality (e.g., NF, USP) of the inactive ingredients should be cited.	Same
Non-compendial Inactive Ingredients	The quality of the non-compendial excipients should, be cited. For novel excipients, additional information may be needed.	By phase 2 the analytical methods and acceptance criteria recognized in official compendia should be referenced. A brief description of the manufacture and control of non-compendial compounds should be provided in the application or appropriate reference provided (e.g., Drug Master File (DMF), NDA).
Manufacturer(s)	The full street address of the manufacturer(s) of the clinical trial drug product should be submitted.	Same
Method of Manufacturing & Packaging	A diagrammatic presentation and a brief description of the manufacturing process should be submitted, including sterilization process for sterile products.	In phase 2 studies, a brief description of the manufacturing procedure in a step wise manner for the unit dose should be provided including sterilization process for sterile products. The description should only focus on the general manufacturing task and specific equipment does not need to be identified.

Specifications & Methods	The tests performed should be indicated (e.g., description, identity, assay, levels of detection). Methods: A brief description of the analytical methods used should be submitted. Acceptance Criteria: Acceptable limits should be provided.	In phase 2 studies, the analytical methods used to perform the test and support the acceptance criteria should be indicated (e.g., dissolution, description, identity, assay, content uniformity, purity, sterility, pyrogenicity/LAL, etc. for sterile products). The complete description of the method and supporting validation data should be available upon request.
Sterility and Pyrogenicity	For sterile products, tests should include compendial (USP) sterility and pyrogenicity/LAL tests.	Same
Microbiology	The test results, analytical data and certificate of analysis should be provided.	Same
Container/Closure System	A general description of the system should be provided including the material of fabrication. In general, specific reference to a Drug Master File (DMF) is not required for this stage of development.	Same
Stability	Only a brief description of the stability study and the analytical methods used to monitor the stability of the drug product packaged in the proposed container/closure system and stress condition should be submitted. Detailed stability protocols are not needed.	Same
Labeling	A mock-up or printed representation of the proposed labeling and labels that will provide to investigators to be used on the drug container should be submitted.	Same
Environmental Assessment	A claim for categorical exclusion may be submitted under 21 CFR 25.24	Same

Phase 3 /pivotal studies are performed after preliminary evidence of effectiveness has been established. They are designed to (1) gather the additional information about the effectiveness and safety that is needed to evaluate the benefit-risk relationship of the drug and (2) provide an adequate basis for the labeling. As mentioned previously, information for the Phase 3/pivotal study section need not be submitted before initiation of the pivotal study(ies). CMC studies can be initiated concomitantly with the clinical studies. The additional information required in Phase 3 is listed in Tables 5 and 6.

Table 5. Phase 3 Requirements For the Drug Substance

Property	Phase 3 Requirements
Description	A full description of the physical, chemical, and biological characteristics of the drug substance should be provided; for example, neutralization equivalents, solubility, partition coefficient, pKa, pH, particle size m.p., specific rotation, stereochemical consideration.
Characterization and Proof of Structure	Supporting evidence to elucidate and characterize the structure should be provided. In general, the following information including spectra should be included: elemental analysis, molecular weight determination, IR, NMR (UV, MS, optical activity.
Manufacturer	All firms associated with the manufacturing and controls of the drug substance (includes contract laboratories for QC and release, contractors for stability studies).
Starting material	Same as phase 2 plus acceptance criteria and analytical methods for the starting material (s) should be provided.
Reagents. Solvents, and Auxiliary Materials	A table listing these reagents should be provided, indicating the grade, specific identity test. minimum acceptable purity level.
Manufacturing Flow chart	Include any updates from phase 2
Manufacturing Description	A general step-by-step description of the synthesis or manufacturing process should be provided, including the batch size, equipment, operating conditions, time and temperature, in-process controls.
Reprocessing	Reprocessing procedures and controls should be provided.
In-process Controls	Should be specified at selected stages in the synthesis or manufacturing process to assure reaction completion and purity should be defined.
Reprocess Controls	These should be described.
Reference Standard Preparation	The synthesis /purification of the reference standard and/or the working standard should be described.
Reference Standard Qualification	Additional analytical tests used to fully characterize the material should be cross referenced to the description/characterization section of the IND.
Analytical Tests & Methods	Appropriate validation information should be provided. Acceptance criteria should be stated.
Purity/Impurity Profile	Impurities should be identified and qualified, as appropriate.
Container/Closure system	A detailed description of the container /closure system used to transport and/or inventory the bulk materials should be described.

Stress Stability Studies	Studies should be included to demonstrate the inherent stability of the drug substance and potential degradation products and the capability of the analytical methods.
Stability Studies and Protocol	A study design listing the tests, sampling time points for each of the tests and the expected duration of the program should be provided. The study should include accelerated and long term storage conditions. The methodology should be described in detail.
Stability data	Each lot number, manufacturing site, and the date of manufacture should contain the storage condition and each individual data point for each test should be reported.

Table 6. Phase 3 Requirements For the Drug Product

Property	Phase 3 Requirements
Components/Composition	Same as phase 3 Drug Substance requirements
Analytical methods for Components	Acceptance criteria should be established and described.
Manufacturers	A listing of all firms associated with the manufacturing and controls of the drug product including: contract manufacture(rs) contract packagers/labeler, contract laboratories for QC and release, and contractors for stability studies.
Method of Manufacturing & Packaging	A general description of the manufacturing process should be submitted, including essential equipment used. A description of the packaging and labeling process of the phase 3 clinical supplies should be provided. Routine tests including microbial should be described
Specifications & Methods	Same as phase 3 Drug Substance requirements
Microbiology	Same as for phase 2 Drug Product
Container/Closure System:	Same as for phase 2 Drug Product

APPROVAL OF NEW RADIOPHARMA-CEUTICALS

If the IND studies indicate that the drug is safe and effective, an NDA is submitted. The approval process to market a radiopharmaceutical for human use begins with the submission of an NDA (Form FDA-356h) which is an application to market a new drug, biologic, or an antibiotic drug for human use. The agency has 60 days from receipt of the application to decide whether or not to accept it. If each required section of the NDA contains enough information to review, the application is "filed." As is done following the IND submission, FDA chemists, pharma-

cologists, and medical officers review the application. After the reviews are completed, any questions the reviewers have posed are provided to the applicant in an Information Request (IR) letter immediately after the review is complete. These questions can be part of either an "approvable" or a "not approvable letter." Once these questions have been satisfactorily addressed, an approval letter can be issued. Just as with INDs, if an NDA is changed prior to approval, an amendment to the application must be submitted.

Changes to the application following approval may require a supplemental new drug application or the changes may be reported to the FDA in the annual report

for that NDA. Supplemental applications may require prior approval before the change can be instituted or it may be a change that can be placed into effect prior to approval by the FDA. Either way, the supplemental application is reviewed by the appropriate FDA personnel and either approved or not approved.

The Federal Food, Drug and Cosmetic Act provides that a new drug may not be introduced into interstate commerce unless the FDA has approved a new drug application for it (21 USC 355). The FDA approves an application for a new drug if the sponsor demonstrates by adequate scientific evidence that the drug is safe and effective for the conditions prescribed, in the drug product's proposed labeling.

The evidence of effectiveness consists of adequate and well-controlled investigations, including clinical investigations. A sponsor is required to demonstrate that the methods used in, and the facilities and controls used for, the manufacturing, processing and packaging of the drug are adequate to preserve its identity, strength, quality, and purity.

In 1997, the Clinton Administration and the US Congress approved major legislation to revise the laws governing the FDA and reauthorize the Prescription Drug User Fee Act (PDUFA). With the passage of this FDA Modernization Act (FDAMA) on November 21, 1997, the FDA has committed to shortened NDA review times. The FDAMA...

- creates a new mechanism for fast-track approval of drugs for serious and life-threatening conditions;
- expands access to investigational therapies and sets up a public data bank on clinical trials for serious or life-threatening diseases and conditions;
- allows manufacturers to distribute peer-reviewed journal articles on off-label uses of drugs approved for other indications, so long as they have first agreed to file supplemental new drug applications for the unapproved uses;
- directs the FDA to publish final guidances within 180 days to clarify the requirements for the approval of supplemental new drug applications;
- authorizes the FDA to approve an NDA on the basis of one well-controlled clinical investigation;
- permits companies to make minor manufacturing changes without waiting for FDA approval;
- requires the FDA to establish guidance for the industry on the kinds of studies for which abbreviated or summary reports can be submitted to support an NDA;
- requires the FDA to follow predicable and consistent procedures in establishing requirements for a new product's marketing approval (meeting with the sponsor concerning clinical trials when requested),

as well as in developing, issuing and using guidance documents;
- establishes that a new human drug manufactured in a pilot or small facility may be used to demonstrate the drug's safety and effectiveness and to obtain its approval prior to scaling up to a larger facility;
- allows the FDA's new regulations for environmental impact statements to satisfy the National Environmental Policy Act's requirements for such statements when a drug is approved for marketing;
- specifies that the FDA cannot regulate pharmacy compounding if the product is compounded by a licensed pharmacist or physician, pursuant to a legal prescription order, for an identified individual;
- gives the FDA, for the first time, a "mission" to promptly and efficiently review clinical research and take timely action on NDA submissions, as well as to ensure that regulated products are safe and effective; and to harmonize regulatory requirements and achieve appropriate reciprocal arrangements with other countries to reduce the burden of regulation;[2]

In addition, the FDAMA of 1997 includes changes to the regulations of Drugs and Biologics Section 121 Positron Emission Tomography. The current FDA regulatory policy has been repealed, including (1) a notice entitled "Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products, Guidance: Public Workshop" [*Federal Register* 60:10594, February 27, 1995], (2) "Draft Guideline on the Manufacture of Positron Emission Tomography Radiopharmaceutical Products: Availability" [*Federal Register* 60:10593, February 27, 1995], and (3) a final rule entitled "Current Good Manufacturing Practice for Finished Pharmaceuticals: Positron Emission Tomography [*Federal Register* 62:19493, April 22, 1997] In the place of these documents, new policy must be developed in accordance with the provisions of this section. Current policy provides (for a period of four years after FDAMA was enacted or for a period of two years after new policies are established) that compounded PET products are not adulterated when they conform to USP standards and monographs in their preparation and specifications, and are exempt from Food, Drug and Cosmetic Act Section 505 (e.g., no NDA required during policy development and implementation period).

Section 122 refers to "Requirements for Radiopharmaceuticals" which requires FDA to issue proposed regulations within 180 days of the enactment of the

FDAMA, and shall be finalized by June 1999. The intended purpose of Section 122 was to clarify the evaluation and approval of diagnostic radiopharmaceuticals. A proposed rule was publisjed on May 22, 1998 [Federal Register 63:28301]. The proposed rule will add a new Part 315 to Title 21 of the *Code of Federal Regulations* (21CFR) and will rename Subpart D of 21 CFR Part 601, adding Sections 601.30 through 601.35. Section 122 does not apply to therapeutic radiopharmaceuticals or PET drugs. Of the changes proposed, one of the more significant is an allowance for indications and claims for effectiveness that are more broad than previously permitted.

Section 127 is the "Application of Federal Law to Practice of Pharmacy Compounding." There are specific exceptions for pharmacy compounding established by this section, which greatly broadens FDA's current highly restrictive enforcement policy. Compounding pharmacies or licensed physicians can produce limited quantities of compounded products. This section exempts pharmacies from certain adulteration (cGMPs), misbranding, and new drug approval requirements. Compounding pharmacies must conform with USP requirements and use USP grade ingredients. Of note, this section specifically does not apply to compounded PET drugs and radiopharmaceuticals. The consensus of opinion is that radiopharmaceuticals (other than PET) can still be compounded, provided that the compounding activities are within the boundaries set forth in the notice entitled "Nuclear Pharmacy Guideline-- Criteria for Determining When to Register as a Drug Establishment" [*Federal Register* 49:24949, May, 1984].

In order to meet these goals and objectives, the FDA has initiated workshops to improve the quality of the original NDA submission which can facilitate evaluation from drug development, to the end of Phase 2 and 3 studies.[3]

APPLICATION OF FDA NEW DRUG REGULATIONS TO THE PRACTICE OF NUCLEAR PHARMACY AND NUCLEAR MEDICINE

Has a a nuclear medicine physician ever called to the nuclear pharmacy and presented a situation such as the following?: "I've been reading about a new radiopharmaceutical in the *Journal of Nuclear Medicine*, and I wanted to know if it is available yet because my practice generally sees ten patients a week that could benefit from its use."

If the radiopharmaceutical mentioned by the physician in this case is an investigational drug, the nuclear pharmacist can respond in one of several ways:

- "No, it is an investigational drug, and probably will not be available for a couple of years."

- "No, it is an investigational drug. However, I would be willing to review literature regarding the drug , including its preparation and use , to determine if we may be able to compound the drug for your patients."

- "No, it is an investigational drug, but I would be willing to assist you in contacting the pharmaceutical company to determine if we might become a site-participant in their investigational protocol."

- "No, it is an investigational drug, but I would be willing to assist you in filing a physician-sponsored IND."

The response and level of support given by the nuclear pharmacist is typically dependent on the extent to which compounding of the drug is required and the specific practice setting of the nuclear pharmacist.

An understanding of the mechanisms by which compounds are tested and ultimately approved as new drugs may provide unique opportunities in the marketplace. Physician-sponsored INDs and clinical trials involving radiopharmaceuticals demand the expertise held by various nuclear medicine professionals. In this environment, nuclear pharmacists, for example, have an opportunity to participate by being active members on an Institutional Review Board, Radiation Safety Committee, Radioactive Drug Research Committee, or as the identified individual needed to prepare the radiopharmaceutical and keep accurate records of drug use.

Ultimately, years are required for a new compound to go from development, through the mandatory pre-clinical and clinical trials, and be released as an approved drug. This approval process affects all nuclear pharmacists (and other nuclear medicine professionals) in their ability to provide appropriate care for patients and compete in the open marketplace. One must hope that the FDAMA, with its sections that are applicable to nuclear phamacy and nuclear medicine, will decrease the time required for diagnostic radiopharmaceuticals to reach the consumer. Ongy time will tell.

REFERENCES

1. Guidance For Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, Center for Dug Evaluation and Research, Food and Drug Administration, Consumer Affairs Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857. An electronic version of this guidance is also available via Internet by connecting to CDER at http://www.fda.cder/guidance/index.htm

2. An electronic summary of the PDUFA Reauthorization Performance Goals and Procedures of the FDA Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, which pertain only to Title 1, Subtitle A of S. 830, the Food and Drug Administration Modernization Act of 1997, is available via Internet http://www.fda.gov/cder/news/pdufagoals.htm

3. Preliminary Draft Guidance for Industry CMC Content and Format of INDs for Phases 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, a preliminary draft guidance distributed for comment purposes only. Consumer Affairs Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, and is available via Internet (Federal Register, May 22, 1998, volume 63, #99, proposed rule).

4. MIRD Primer for Absorbed Dose Calculations, prepared by R. Levinger, T Budinger and E Watson, 1991, The Society of Nuclear Medicine, New York, NY.

QUESTIONS

1. What primarily distinguishes radiopharmaceuticals from conventional drugs?

    a. Conventional drugs are therapeutic
    b. Conventional drugs come in tablets
    c. Conventional drugs do not contain a radioisotope
    d. Conventional drugs are sold in drugstores

2. What is the dominant physical characteristic affecting the commercial development of radiopharmaceuticals based on fluorine-18?

    a. fluorine is a difficult element with which to work
    b. fluorine-18 has a 110-minute half-life
    c. fluorine does not behave exactly like hydrogen
    d. fluorine in water as fluoride adds too much "carrier" to the drug environment

3. Which of the following is **not** a typical ingredient in a Tc-99m based cold kit?

    a. reducing agent
    b. bulking agent
    c. transfer ligand
    d. dispersing agent

4. Which statement is **not** true for single-photon diagnostics and PET radiopharmaceuticals?

    a. they are all classified as drugs by the FDA
    b. they all use radioisotopes
    c. they all consist of two parts: a hot generator eluate and a non-radioactive cold kit
    d. they are all imaged using a nuclear medicine camera.

5. What is the first step in the design of a new radiopharmaceutical?

    a. the R&D process to identify a lead compound
    b. running a molecular modeling computer program
    c. getting management support for a new project
    d. surveying the scientific literature for similar work

6. What pharmacology consideration is unique to radiopharmaceuticals?

    a. adding carrier to the drug formulation
    b. making absorbed dose measurements
    c. determining absorption by the gastrointestinal tract
    d. identifying drug metabolites

7. The FDA regulatory approval process begins with:

    a. the first good animal experiment.
    b. preparation of an informed consent form.
    c. submission of an IND.
    d. approval at an institutional review board.

8. FDA regulations are contained in what document?

    a. the United States Pharmacopeia
    b. the Peterson's Giude
    c. the Journal of the American Medical Association
    d. the Code of Federal Regulations

9. An FDA Guidance is **not**:

   a. just as enforceable as a law.
   b. the FDA's interpretation of federal regulations.
   c. written by the FDA when there is a perceived need for additional explanation.
   d. updated as necessary.

10. Which of the following specifications is **not** unique for radiopharmaceuticals?

   a. radioisotopic composition and purity
   b. maximum specific activity
   c. chemical purity
   d. physical decay scheme for the radionuclide

11. Which of the following is not required as phase 2 clinical studies begin?

   a. description of the starting material
   b. description of in-process controls
   c. street address of the manufacturer of the clinical trial materials
   d. a detailed flow chart showing steps in the manufacturing process

12. Before Phase 3 clinical trials begin which of the following is **not** required?

   a. proof of structure of the drug substance
   b. printed representation of the proposed labeling
   c. list of potential types of customers
   d. stress stability studies

13. The FDA has how many days from receipt of an NDA to accept the application?

   a. 120
   b. 365
   c. 60
   d. 30

14. A new molecular entity is:

   a. a generic drug produced by a new company.
   b. not a factor with radiopharmaceuticals.
   c. a compound that has not previously been used as a drug in the US.
   d. a previously known compound that has new clinical uses.

15. Phase 1 protocols are directed primarily at:

   a. providing an outline of the investigation.
   b. determining the dose.
   c. determining if the drug will be efficacious in patients.
   d. evaluating the safety of the investigational drug in humans.

16. The FDA can place a clinical hold on human studies only when:

   a. there is a safety concern or insufficient data to make an evaluation of safety.
   b. the animal studies are incomplete.
   c. the chemical structure of the drug substance is unknown.
   d. there is no environmental assessment.

17. The drug substance for a Tc-99m based radiopharmaceutical is:

   a. the pertechnetate because it contains the radiolabel.
   b. not known because there are no stable isotopes of technetium.
   c. the technetium complex.
   d. everything in the reconstitution vial that is injected for imaging.

18. Which of the following is **not** a criteria used to define a starting material?

   a. the material is commercially available
   b. the material is well-defined in the chemical literature
   c. the material is not stable
   d. the material is incorporated in the drug substance

19. For cold kits based on nuclear generators which of the following is true?

   a. two NDAs are required - one for the cold kit and one for the generator
   b. an NDA is required for the cold kit because it yields the drug, but not for the generator
   c. generators that come from Europe don't need an NDA
   d. generators need an FDA "good practices" (GP) letter

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20. The Food and Drug Modernization Act of 1997:

    a. specifies that radiopharmaceuticals be approved within two years.

    b. allows manufacturing of PET agents without an NDA.

    c. authorizes the FDA to approve an NDA based on one well-controlled clinical study.

    d. requires the FDA to help in the preparation of drug label wording.

21. Drugs are **not** defined as agents used to:

    a. diagnose disease.

    b. mitigate disease.

    c. prevent disease.

    d. supplement diet.

22. The FDA form used for IND application is:

    a. DHHS-123.

    b. FDA-1571.

    c. IRB application.

    d. PDUFA-1.

23. The FDA describes proposed rule making in:

    a. government brochures.

    b. The Federal Register.

    c. newspaper advertisements.

    d. letters to medical center directors and pharmaceutical company presidents.

23. In the context of FDA drug approval. CMC is an acronym for:

    a. Criteria, Methods and Constraints.

    b. Congressional Mediation Conditions.

    c. Clinical Metabolic Center.

    d. Chemistry, Manufacturing and Controls.

25. Section 127 of the FDA Modernization Act of 1997:

    a. exempts pharmacists from needing a license.

    d. exempts pharmacists from conforming to USP requirements if directed by a physician.

    c. allows pharmacies to produce limited quantities of compounded products.

    d. provides for criminal prosecution of pharmacists who practice PET without an NDA.