

Radiopharmaceuticals for Drug Development: United States Regulatory Perspective

Henry F. VanBrocklin*

Center for Molecular and Functional Imaging, Department of Radiology, University of California San Francisco, San Francisco, CA 94107, USA

Abstract: Imaging with radiopharmaceuticals is playing an increasingly important role in the development of new drugs. At nearly every step of the process imaging may be used to assess the status of the candidate drugs and assist in determining the lead molecules for further evaluation. Incorporating imaging studies into the paradigm may ameliorate the temporal and economic cost of drug development. Since 1975 radiopharmaceuticals have been regulated as drugs and all human studies must be carried out under an investigational new drug (IND) or radioactive drug research committee (RDRC) protocol. The FDA released the exploratory IND guidance in 2006 to highlight the flexibility in the IND process while trying to stimulate new drug entry into the approval pipeline. The exploratory IND also provides a lower threshold for radiopharmaceutical and candidate drug first in human studies, using the microdosing concept, that may not be conducted under an RDRC protocol. The RDRC mechanism permits the basic research studies with limited dose and numbers of subjects. The RDRC regulations are 30 years old and the full IND process remains burdensome for radiopharmaceutical development. Therefore, it is essential that the regulatory framework permit the approval of radiopharmaceuticals for use in humans that is commensurate with the safety and applications of the probes.

INTRODUCTION

Beyond diagnosing and staging disease, monitoring progression or therapeutic intervention, imaging is playing an increasingly important role in the drug discovery and development process. Nuclear imaging, positron emission tomography (PET) and single photon emission computed tomography (SPECT), with radiolabeled molecular entities, radiopharmaceuticals, permits the visualization of the distribution of potential drugs as well as interrogating their effect on disease, organ systems and the whole body. Imaging probes may be applied in two ways to drug development, i) to define the pharmacokinetic (PK) properties of labeled drug candidates or ii) to assess the pharmacodynamic (PD) properties of new drugs. Molecular imaging's role in drug discovery and development has grown significantly over the last decade and it will continue to have a major impact on the assessment and profiling of new drugs for the foreseeable future.

Since 1975 radioactive labeled entities, small molecules and biologics, have been considered by the United States Food and Drug Administration (FDA) to be drugs and are regulated as such. In spite of the fact that imaging probes, by their very nature, are "tracers" with minimal mass and no expected pharmacological or toxicological properties, they must undergo extensive safety evaluation prior to approval by the FDA. All human studies involving radioactively labeled molecules, unless exempt, must be performed under FDA guidelines using either an investigational new drug (IND)^a or Radioactive Drug Research Committee (RDRC)^b approval mechanism. This article describes the United States regulatory pathways that are involved to permit the use of new and existing radiopharmaceuticals in the drug discovery and development process.

The Cost of Drug Development

The development of new drugs is a lengthy and expensive process with significant barriers to success. The price tag associated with bringing new drugs through the discovery and developmental

process has been recently calculated, based on 68 drugs, to cost between \$1.0 – 2.0 billion USD [1]. While the validity of this educated estimation has been challenged and reinforced [2, 3], there is no denying the fact that the economic and temporal cost of drug development impacts the ability to effectively produce new drugs that will successfully treat intractable diseases improving patient quality of life while minimizing undue healthcare costs. Molecular imaging approaches have the potential to shorten the drug development process timeline and reduce associated costs.

According to research conducted at the Tufts Center for the Study of Drug Development (CSDD) the average time to move a new chemical entity from discovery through development and the three phases of clinical trials to get full Food and Drug Administration (FDA) approval to market the drug increased from 7.9 years in the 1960's to 12.8 + years in the 1990's [4, 5]. It is not unheard of for this process to take up to 15 years. The most time consuming aspects of the process are the early discovery phase involving screening a large numbers of candidate compounds to define a lead class or classes of molecules and phase III clinical trials that involve sizeable cohorts of patients in multi-center trials [1, 4-7]. A reduction of the development time by 25% would produce a 16% cost savings [8].

Attrition from the development pipeline also impacts the numbers of new entities that make it to market. It has been estimated that for every 5000-10000 compounds that enter the pipeline in the discovery phase only about 0.1% (~ 5 compounds) become fully approved drugs [7]. Early in the process the attrition may be due to the inability of the compound to obtain adequate concentrations in target tissues, inability to bind to a receptor *in vivo*, or demonstrate inappropriate absorption, distribution, metabolism and excretion (ADME) characteristics. It has been reported that up to 25% of all entities entering the clinical phases reach the approval stage [9]. Increasing this to 33% would produce up to a 50% overall cost savings. The decision to remove candidate drugs from the clinical phase pipeline is very difficult especially in the later phases with a decade of investment. Developing reliable, validated and reproducible imaging biomarkers is necessary to confidently support the decision making process. Earlier removal from the pipeline will produce significant programmatic cost savings and may permit the evaluation of alternate chemical entities.

In the current drug development paradigm, therapeutic efficacy is not evaluated until phases II or III. Imaging biomarkers, however, may provide a means of assessing initial efficacy early in phase I. With validation and experience one may be able to confidently make critical decisions regarding continuation of the clinical trials or redesign a late phase I/II experiment to support or challenge the

*Address correspondence to this author at the Center for Molecular and Functional Imaging, Department of Radiology, University of California San Francisco, 185 Berry Street, Suite 350, San Francisco, CA 94107, USA; Tel: 415-353-4569; Fax: 415-514-8242; E-mail: henry.vanbrocklin@radiology.ucsf.edu

^a 21CFR312 Investigational New Drug Application. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312> Accessed October 2, 2007.

^b 21CFR361.1 Radioactive Drugs for Certain Research Uses. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=361.1> Accessed October 2, 2007.

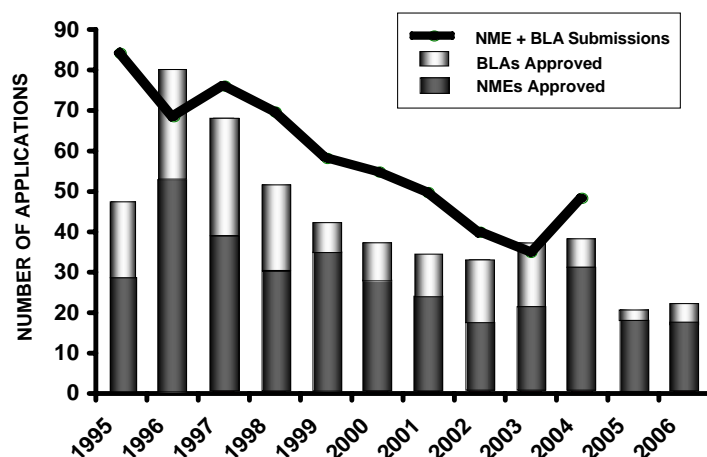


Fig. (1). Annual number of New Molecular Entity (NME) applications and Biologic License Applications (BLAs) submitted and approved by the FDA from 1995-2006. Data collected from the FDA website.^{c,d} The data for submitted applications were not available for 2005 and 2006. In 2004 BLAs for therapeutic biologics were transferred from CBER (Center for Biologics Evaluation and Research) to CDER (Center for Drug Evaluation and Research). These numbers are not reflected in the graph to preserve the annual comparisons for CDER data.

continuation of the development program. Confidence in the data is the key to being able to halt the clinical trials.

The therapeutic response rate is also an important criterion in drug development. In many cases the response rate of targeted therapeutics is only 10-20%. Even when patients expressing the desired target are selected for treatment the response rate is not as high as one would expect. A good example is the treatment of HER2 positive breast tumors with trastuzumab (Herceptin). HER2 is overexpressed in 25-30% of breast tumors. Of those patients with HER2 positive tumors receiving trastuzumab as their first therapy only 25% respond to the treatment. Those HER2 positive patients that are administered trastuzumab as second or third line treatment only demonstrate a 15% response [10]. Thus, while expressing the target may increase the likelihood of response, there is no guarantee that it will happen. Rapidly identifying those patients that fail on one drug may actually increase their chances of response and overall survival by administration of alternative therapies. This may also improve quality of life by discontinuing the administration of unsuccessful medications that have significant side effects. Functional imaging probes may visualize metabolic and cellular architecture changes long before these are manifested or may be measured.

The FDA's Critical Path Initiative

Over the last decade there has been a significant decline in the number of new molecular entities (NMEs) and biologics license applications (BLAs) submitted to the FDA. Correspondingly, the number of new approvals also declined. Fig. (1) shows the annual trend of total NME and BLA submissions over the last decade as well as the approvals by each type of application. The total number of submissions and approvals peaked in the mid -1990's and have declined ever since. Strikingly, the number of approvals for 2005 and 2006 are 25% of the number approved in 1996. This significant decline in new drug approvals was a call to arms for the FDA. In their 2004 report "Innovation or Stagnation"^c the agency declared that "The medical product development process is no longer able to keep pace with basic scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path."

The FDA developed an action plan called the "Critical Path Initiative" (CPI).^{c,d} The CPI represents a framework for facilitating the entire drug discovery and development process from inception to approval. Not only is the FDA reworking the way that they approve drugs, reducing the time for approvals, but they are also leveraging scientific advancements in bioinformatics, genomics, proteomics, material science and medical imaging to overhaul the entire process to stimulate NME and BLA submissions. One of the recent FDA initiatives that has been implemented, impacting both therapeutic drug development and well as imaging probe development, is the establishment of the Exploratory Investigational New Drug (xIND)^e application.^f One of the hallmarks of this xIND mechanism is the concept of microdosing. Initial studies with new drug and radiolabeled compounds in humans are fostered by a reduction in costly toxicity data needed for approval, compared to that required for a full IND, allowing one to assess preliminary PK/PD in humans early in the development timeline. This will allow earlier go-no go decisions and enhance the pool of selected therapeutics that will proceed to the more costly clinical trial phases of development. This updated IND process also facilitates first-in-human studies for radiotracers that may eventually be validated for use in the drug development schema.

The Regulatory Process for Imaging Agents

With the implementation of the CPI within the FDA, the regulatory pathway for radiopharmaceuticals for medical imaging has changed over the last two years. The most significant change was the introduction of the microdosing concept lowering the threshold for performing first-in-human (FIH) studies, thus enabling the evaluation of many new radiolabeled probes in humans prior to extensive and costly toxicology studies [11, 12]. The current flow of radiopharmaceuticals through the regulatory process is shown in (Fig. 2). Once a radiopharmaceutical has been evaluated in preclinical models and selected for studies in humans the researcher must determine whether this compound, radioactive or non-radioactive, has ever been administered to humans. If the compound has been not been in

^c Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, HHS, Editor. 2004, Food and Drug Administration. pp31 <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html> Accessed August 5, 2007

^d http://www.fda.gov/oc/initiatives/criticalpath/presentations/bio200501_files/textonly/slide4.html accessed October 8, 2007.

^e xIND is not an official abbreviation for Exploratory IND. There is an Emergency IND that is sometimes abbreviated EIND. In order to avoid possible confusion xIND was chosen in this article to differentiate between a full IND and an exploratory IND application.

^f Office of New Drugs in the Center for Drug Evaluation and Research (CDER), FDA, Department of Health and Human Services, Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies 2006. <http://www.fda.gov/cder/guidance/7086fn1.htm> accessed August 5, 2007

humans then human studies would need to be covered under an IND, exploratory (xIND) or conventional (IND), otherwise with some prior human exposure the radiolabeled compound may be evaluated under an FDA-authorized RDRC approval, with a few caveats detailed below. An example of a radiopharmaceutical that may be assessed under an RDRC approval is [^{11}C]choline, where a carbon-12 containing methyl group is isotopically replaced by a carbon-11 methyl group. These two compounds are biologically identical. As non-radioactive choline is an endogenous essential building block for cell membrane synthesis and it is ubiquitous in humans, the trace amount of non-radioactive choline that is produced with [^{11}C]choline is orders of magnitude below the toxic threshold, therefore, within the guidelines and depending on the study, RDRC and institutional review board (IRB) approval may be all that is necessary for the evaluation of this compound in humans. On the other hand, [^{18}F]fluorocholine, where one of the methyl hydrogens is replaced with a fluorine-18, is not endogenous in humans and would be considered a new molecular entity. As such [^{18}F]fluorocholine studies would require minimal toxicity studies and FDA approval of an xIND or IND prior to FIH studies. As will be discussed below there are scenarios where an IND may be required to evaluate or use radiopharmaceuticals in humans.

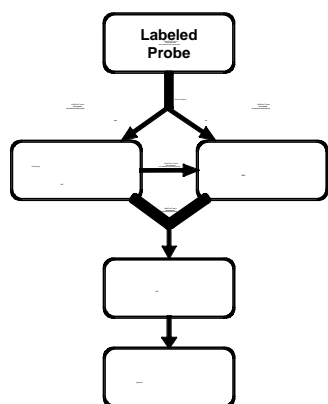


Fig. (2). Flow diagram showing the regulatory pathway for the approval of radiopharmaceuticals.

Once the xIND study is complete and one desires to conduct further investigations with the radiopharmaceutical there are two choices available to proceed. Either further research studies are carried out under an RDRC protocol or an IND is submitted to the FDA. RDRC studies would be undertaken when additional evaluation of the radiopharmaceutical is preferred and the probe is not being moved towards full FDA approval. Radiopharmaceuticals that will be brought forward for approval and marketing will be covered under the IND process through the clinical evaluation phases of development. As shown in Fig. (2) radiopharmaceuticals previously studied under RDRC protocols may be converted to an IND application to continue the process toward approval.

Exploratory Investigational New Drug

The traditional approach for drug development involves the screening of thousands of compounds in search of a lead structure or structures that belong to a class or classes of molecules with desirable pharmaceutical characteristics against the chosen target. The lead compounds are further evaluated *in vitro* and a handful are selected for preclinical evaluation in animals. Safety and efficacy studies in animals generally yield a lead candidate that will be taken through the clinical phases of development. Extensive pharmacological and toxicological testing, multiple doses in multiple species, at least two,

is undertaken on this single lead compound prior to submission of the IND application to the FDA. The cost of the pharmacological and toxicological package alone for an IND submission can easily reach \$0.4-0.5 M USD. Additionally, several years of discovery and preclinical development has already been expended to get to the clinical phases. This represents significant time and financial resources that are now pinned to the success of one compound making it through the clinical phases. The estimates for success of a new drug reaching the new drug application (NDA) approval stage from phase I range from 10-25% [1, 9]. If the lead compound fails in clinical trials there may be a second or third candidate from the preclinical studies remaining to be tested. Depending on the cause of failure of the first compound and the resources remaining for the project, an IND may be filed on a second compound. This bottleneck in the drug development process may kill an entire drug development program with drug candidates left on the bench that may never be tested in humans for their intended target.

As part of the CPI the FDA noted that there had always been significant flexibility in the IND program to tailor trials to maximize the ability to test multiple candidate drugs in the early clinical phases. Many drug developers did not realize that this flexibility existed. In 2006 the FDA developed guidance documentation for xIND submissions describing the flexibility by indicating the types of IND information needed for agency submission and the types of studies that may be performed under this mechanism. It is important to point out that no new regulations were implemented.⁵ The xIND falls under the IND regulations set forth in the Code of Federal Regulations Title 21 part 312 (21CFR312).^a The guidance provides information about the requisite chemistry and manufacturing of the candidate products, drugs and therapeutic biologics, as well as the required pharmacology and toxicology information from preclinical studies.

A key component of the xIND guidance is incorporation of microdosing into the development paradigm. These 'phase 0' studies, first introduced in 2004 in an European Medicines Agency (EMA) position paper⁹, occur before the phase I safety and dose escalation studies. The definition of microdose is given as "less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect of the test substance with a maximum dose of ≤ 100 micrograms or, in the case of biologics, ≤ 30 nanomoles". These studies are intended to limit human exposure and provide no therapeutic or diagnostic information.

The types of exploratory studies that would be covered under an xIND would include determination of the mechanism of action such as receptor binding, pharmacokinetic properties (ie. hitting the target), evaluation of a group of candidates to select a lead for further clinical trials and, lastly, evaluation of candidate PK using imaging techniques. The risk to human subjects is minimized by using a microdose of test compound well below the expected toxic threshold. As a result the supporting preclinical data required to back an xIND application is significantly reduced. Given the scenario where multiple compounds from the same class emerge from preclinical testing, an xIND study would allow the evaluation of all of these compounds without completing an expensive pharm/tox package. The proposed xIND study would dictate whether single-dose or multiple-dose toxicity studies are warranted in the application.

There are a few other caveats to the phase 0 studies. First the number of subjects or patients (e.g. 5 - 30) and the dosing regimen are limited. The suggested limitation for dosing schedule of the candidate pharmaceutical is about 7 days. Certain products are excluded from an xIND including human cell or tissue products, blood and blood proteins, vaccines and devices. It is also suggested that xIND studies would not be performed in pediatric patients as well as pregnant or lactating women.

⁵ Committee for Medicinal Products for Human Use (CHMP), EMA., Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose. <http://www.emea.europa.eu/pdfs/human/swp/259902en.pdf> Accessed October 3, 2007, 2004.

xIND AND RADIOPHARMACEUTICALS

There is specific reference to imaging in the xIND guidance.⁶ In section III.C.1 entitled “*Clinical studies of pharmacokinetics or imaging*” the guidance provides an example of the pharmacologic and toxicologic information needed to support an xIND application for a radiopharmaceutical. Most if not all radiopharmaceuticals would fall into the microdosing category as there is no expected pharmacological or toxicological effect from the labeled probe. Thus, the guidance supports a single-dose single mammalian species 14-day toxicology test. The species is chosen based on *in vitro* metabolism or PD data. Both sexes would be included in the study and an interim necropsy on day 2 and final necropsy on day 14 would be the endpoints. Hematology, histopathology, clinical chemistry, and body weight are required elements of the information. The toxicology study dose should produce a minimal toxic effect or provide a margin of safety, typically 100X the human dose given to the study animal. The dose should also be scaled from the human to the animal subject using a body surface area calculation or PK/PD modeling. Since the initial radiopharmaceutical study will be a single microdose administration, genetic toxicology and safety pharmacology studies are waived.

While there are no statistics released regarding the xIND use in the 18 months since this guidance was introduced, the lower barrier to FIH studies for radiopharmaceuticals has attracted several xIND applications. Results from some of these studies should be forthcoming in the literature.

Overall, the xIND guidance provides clarifying examples of the types of studies that the FDA will support under the IND application. However, examples of every type of study that would be accepted have not been presented and one is encouraged to engage the FDA to determine the degree of latitude that one may have in these phase 0 studies.

Radioactive Drug Research Committee

Basic research studies on radiopharmaceuticals that are “generally recognized as safe and effective” (GRASE) have been carried out under RDRC approval since 1975. The RDRC regulations may be found in Title 21 part 361.1 of the Code of Federal Regulations, entitled “Radioactive drugs for certain research uses” (21CFR361.1).^b The RDRC is an institutional body that reviews research protocols for scientific and technical merit. An overview of the RDRC program from 1975-2004 has been recently reported [13]. As of 2003 there were 84 active RDRCs in the United States.

In order to be GRASE a radiopharmaceutical is limited in terms of pharmacological and radiation dose. The mass associated with the radiopharmaceutical must “be known not to cause any clinically detectable pharmacological effect in human beings”. As a result of this limitation FIH studies may not be carried out under an RDRC protocol. Typically RDRCs require published human studies involving the tracer to be evaluated before approving a protocol. The dose limitation requires that the smallest radiation dose needed to obtain meaningful data from the study be administered to the study subject. The maximum allowable single dose to the whole body, blood-forming organs, lens of the eye and gonads is 30 mSv (3 Rem) with a maximum annual or total dose of 50 mSv (5 Rem). The maximum single dose and total annual dose to all other organs is 50 mSv (5 Rem) and 150 mSv (15 Rem), respectively. There is also a significant radiation dose limit on studies involving research subjects that are less than 18 years of age. The dose may not exceed 10% of the adult doses reported above. Additionally, all radiation dose associated with the study must be included in the total study dose. This means that the CT dose from a PET/CT study must be included in the total and this total may not exceed the maximum limits set forth in the regulations.

The types of studies that may be conducted under an RDRC approved protocol are also regulated. The research must be basic in

nature and may include the evaluation of the radiopharmaceutical PK, metabolism and excretion. The distribution of a radiopharmaceutical to evaluate human physiology, pathophysiology or biochemistry is permitted as long as the studies are not for diagnostic or therapeutic benefit. Safety and efficacy studies are not permitted under these regulations. An example of a study that is permissible under RDRC would be the brain distribution of [¹⁸F]FluoroDOPA relative to subject age or neurodegenerative disease.

The RDRC may not approve protocols that require more than 30 subjects. If more than 30 subjects need to be studied and may be justified by the researcher then a special summary form is submitted to the FDA for review. A pediatric consultant to the RDRC must review studies involving minors under 18 years old and a special summary must be submitted to the FDA. In addition all adverse reactions “attributable to the use of the radioactive drug” must be reported immediately to the FDA. It is interesting to note, however, that over the 30 years since the inception of the RDRC regulations with an estimated 60,000 subjects enrolled in the studies not one adverse event has been reported [13].

The regulations also stipulate the constitution of the RDRC with appropriate expertise to review the protocol applications. The committee must have at least 5 members. Three of those members must be a nuclear medicine physician, a qualified individual with radiopharmaceutical preparation experience, and a radiation dosimetry / radiation safety expert. The remaining members must have experience and qualifications in disciplines related to nuclear medicine.

PERSPECTIVE

Radiopharmaceuticals have always been treated as drugs by the FDA and as such the barriers to move radiolabeled probes through the development process has been slow. The cost of developing diagnostic imaging agents through the NDA approval stage has been estimated at \$100-200M USD [14]. The market for these radiopharmaceuticals must be sufficiently large enough to support the development otherwise the cost per dose would have to be prohibitively expensive. One of the ways that the market could be increased for radiopharmaceutical application would be to use these probes in the development of new drugs, patient stratification or monitoring treatment. The most likely scenario is that most radiopharmaceuticals will be used for various applications without ever receiving full FDA approval. This is certainly the case today where only a small number of tracers have approved by the FDA.

The biggest application for new radiopharmaceuticals is currently in the area of drug development. There are a number of large pharmaceutical companies and contract research organizations (CROs) that have invested in small animal imaging equipment to use in their drug discovery and development programs. Given that the radiopharmaceutical development pathway may be as lengthy as that for the new drug, one of the best ways to incorporate imaging into the drug development paradigm is parallel development of the imaging probe. This way the probe is available for imaging studies in the clinical phases and one does not have to wait for human approval and validation of the radiopharmaceutical. Therefore, it is important to have a process that permits the approval of radiopharmaceuticals for use in humans that is commensurate with the safety and intended application of the probes.

The FDA recognized over the last few years that the drug development process under the IND mechanism was not keeping pace with the significant advancements in pharmaceutical science. The process had become so limiting that it was constricting the flow of new drugs in the pipeline. With the development of the critical path initiative the FDA has started to stimulate the process to bring more new drugs into the approval pipeline. As part of this process they developed the xIND guidelines the lowers the threshold to FIH studies not only for new drugs but also for new radiopharmaceuticals.

This process improvement has already resulted in an increase in the number of new radiopharmaceuticals evaluated in humans.

Given the flexibility that has been exemplified in the IND process by the xIND guidance and concomitant approval process, the ability to use radiopharmaceuticals that have been studied previously in humans under an xIND in an IND application for a new drug will begin to rise. Certainly validation studies of radiopharmaceuticals will be conducted under the IND process. One would hope that to get approval for these validation studies that the full pharmacological and toxicological package required for a new drug would not be required for a radiopharmaceutical IND. This requirement would stifle the promulgation of radiopharmaceuticals as potential biomarkers for drug assessment. Additionally, flexibility must be involved when an unapproved radiopharmaceutical is applied in humans to measure the therapeutic effect of an unapproved new drug. Current guidelines allow this combination only under an IND not RDRC protocol. These studies are important not only to validate that the radiopharmaceutical may measure the therapeutic response but also to provide valuable information about the efficacy of the new drug. This is important given that a majority of the radiopharmaceuticals, especially for PET, do not have FDA approval.

The RDRC process has served the academic community well for the last 30 years. However, the regulations were written in 1975 and many things have changed since then. The FDA held a meeting over 3 years ago to engage the RDRC community and to gauge the types of changes that would be necessary to bring the regulations into the 21st century. The FDA realizes that the regulations need to be revised yet it is taking a considerable amount of time to make these changes. The most important changes that need to be addressed are the radiation dose limits and the limitation of the dose for subjects under the age of 18. The current limitation is the organ dose limits are too confining and that the organ doses would be exceeded long before the whole body dose reached its maximum. The disparity in these values could be remedied by switching to "effective dose equivalent" and "effective doses". These measures take into consideration years of

experience relating to whole body exposure to radiation and apply weighting factors to the organ doses to determine the effective dose. The second issue relative to the RDRC is the limitations for dose to minors. This limitation poses issues related to federal funding especially from NIH where inclusion of children in studies is mandated. Currently, an IND submission is required in order to study a radiopharmaceutical in children. This issue must be addressed to allow the basic science evaluation of radiopharmaceuticals in children under an RDRC approval as is currently allowed in adults.

The use of radiopharmaceuticals in the drug development pathway is increasing rapidly. There is mounting evidence that the use of radioprobes will assist with making critical decisions that will ultimately impact the timeline and cost of new drug development. It is imperative that the regulatory framework keeps pace with the changes in the scientific advances such that the radiopharmaceutical pipeline continues to grow and provide new tools for the further advancement of new drugs.

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