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CENTER FOR DRUG EVALUATION AND RESEARCH

RADIOACTIVE DRUGS FOR CERTAIN RESEARCH USES

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8:00 a.m.

Advisors and Consultants Conference Room 1066
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Rockville, Maryland

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P R O C E E D I N G S

Welcome and Opening Remarks

DR. MILLS: Good morning. I am Dr. George Mills. I am the Director of the Medical Imaging Radiopharmaceutical Drugs Products Division, within the Center for Drugs, and I am introducing and welcoming you to this meeting this morning.

A couple of housekeeping events I am going to take you through first, number one is that inevitably, when everybody passes through in getting your badges, somebody leaves their keys behind. I have a set of keys; they are for a Saturn. So, they will be up here when somebody is looking for them. Number one.

Number two, I have been asked several times this morning about where the restrooms are and the vending machines. Out through the door, on your left you will find the restrooms and the vending machines. Location of public phones, there is one located up on the Parklawn Drive entrance upstairs.

Lunch--there is going to be a flyer out on

the table listing restaurants within walking distance of the building, available with other handouts that are on the table in the hallway. There is no food or drink allowed in this conference room.

Turn off your cell phones during the meeting. Inevitably, somebody has one that is on. Try at least to keep it on the buzzer if you are going to have it.

Turn in your visitor badges at the end of the meeting in the box located at the table in the hallway, and know that badges need to be turned in if you are going to leave the building for lunch and you have to sign back in.

Now, over the lunch hour we will actually have a presentation that may be of interest to some people to hear. It is going to be Dr. Diane Jorkawski, from Pfizer Corporation, who will be presenting, the title, "The Use of Imaging in Early Drug Development Leveraging for Productivity." So, lunch will begin from this room at 11:15 and we will come back to this room for this meeting at

1:30. Her presentation will begin at noon and conclude at 1:30, just before this meeting reconvenes.

So, let me begin now in terms of welcoming you to our meeting today. It is a public meeting, as noted in the Federal Register. It is titled "Radioactive Drugs for Certain Research Uses." This morning, in terms of my introductory comments, I am going to take you through the stated meeting objective and the topics that we will be posing to you for public comment; the schedule and general format of the meeting today; and then give you a very brief RDRC participation history that we have seen over the past 29 years.

Our meeting objective today, we are seeking public input on the need to modify the conditions set forth in 21 CFR 361.1 that would ensure safe use of radioactive drugs for basic research purposes, without an investigational new drug application, IND.

This is in light of the numerous scientific and technological developments that have

significantly impacted the use of radioactive drugs since the RDRC's regulations were adopted in 1975.

Now, question topics in general today are five. First, the radiation dose limits for adult subjects, should they be modified as currently presented in the regulation?

Number two, the assurance of safety for pediatric subjects. Number three, quality and purity of radiopharmaceuticals and the issues associated with that. Number four, the exclusion of pregnant women in RDRC trials and, number five, RDRC membership and administrative issues.

This morning's session will have first, number one, the RDRC versus IND background that will be presented by the FDA. Then, examples of appropriate RDRC studies for basic research. Our third area, no pharmacological effect as related to this regulation. The fourth will be the radiation dose limits as present in the regulation. And, number five, studies in pediatric subjects.

The afternoon session, beginning at 1:30, drug quality and purity issues; the pregnancy

issue; and RDRC membership and administrative issues.

For written and electronic comments beyond the extent of today's meeting, you can submit written or electronic comments by January 16 of 2005 to the Division of Dockets Management. This is all outlined in the Federal Register notice. I will briefly take you through the mechanisms that you can utilize to present those comments to us. First of all, in the Federal eRulemaking Portal that you can enter, number two, the agency web site has an entry point. Number three, you can submit by E-mail. Number four, by fax and, number five, by mail, hand delivery and courier. Again, all of these are presented in the Federal Register notice. All of these will be in my slide handout, which is at the back table also.

Now a brief summary of RDRC's history and activity that we have seen, since 1975201 RDRC committees have been established. From our most recent complete records that we have, in 2003, 84 RDRCs are active, 30 of which though are reporting

no active studies. There are 284 active studies in 2003 and they enrolled a total of 2,797 subjects. There are 120 radioactive research drugs in use in those trials, and 73 of the 120 are positron-labeled drugs.

This is a busy table but let me just give you the highlights of this. We see two breaks in terms of the radionuclides that have been utilized. On the left you will see the imaging radionuclides, both positron and gamma emitters. On the right, the non-imaging radionuclides. We are showing you the activity, the non-imaging radionuclides, beta emitters are 18.4 percent, and tritium, the leader beyond that. 12.4 percent.

If we look on the imaging radionuclides with the positrons, which accomplished 77 percent of all the activity, C-11, F-18 and oxygen-15 are the leading items that we see with positron activity. For the gamma emitters, only 4.5 percent of this activity, and here technetium-99m, in frequent use in common nuclear medicine, is at only 2.5 percent. I-123 is the second most common

imaging technique.

Recent issues that have come through the RDRC, and we will be elaborating somewhat more in the afternoon on this, number one is pediatrics--two studies approved in this past year, one of which was determined actually to be a safety and efficacy study and that was moved from the RDRC activity under IND.

Then, the quality of radioactive drugs--materials labeled as biohazard have been administered under the RDRC, without controls in place, to ensure that the material was free of viral contamination. A second issue was absence of production standards and quality control have led to the administration of an unknown compound to two subjects.

With that, I am going to take you to our first speaker this morning to follow, and that is Dr. Lynn Panholzer and her topic will be the activity for RDRC trials versus INDs. Lynn?

RDRC vs. IND

DR. PANHOLZER: Good morning. This

morning I will be reviewing the differences between conducting research with radioactive drugs under the oversight of a radioactive research committee versus under an investigational new drug application.

There are three ways to study radioactive drugs in human subjects. The first way is under an investigational new drug application or IND, and this is the way most new drugs are studied in humans. The regulations governing IND research are found in Title 21 of the Code of Federal Regulations, Part 312.

It may also be possible to study a radioactive drug without an IND if the study meets the criteria for exemptions that are described in 21 CFR 312.2. For example, a radioactive drug that is already lawfully marketed in the United States could be studied without an IND under certain conditions.

The third way to study radioactive drugs in humans is under 21 CFR 361.1, which allows that radioactive drugs for certain research uses can be

classified as generally recognized as safe and effective and, therefore, can be studied without an IND.

The mechanism for studying radioactive drugs under 361.1 began in 1975 when a final rule was published in the Federal Register that established that all radioactive drugs are either new drugs or are generally recognized as safe and effective depending on their use. Those radioactive drugs classified as new drugs are subject to new drug requirements of the FD&C Act, including the submission of an IND.

The determination of a radioactive drug as generally recognized as safe and effective is made by the FDA, and radioactive drugs can be classified as generally recognized as safe and effective if they are used for certain research uses under specified conditions, and 361.1 was established to specify those conditions of use under which a radioactive drug could be recognized as generally recognized as safe and effective, also known as GRASE. Drugs classified this way are not

considered new drugs and, therefore, are not subject to new drug requirements such as IND regulations.

In order for a drug to be considered generally recognized as safe, the final rule specified that the amount of the drug to be administered has to be known not to have any clinically detectable pharmacological effect on humans. And, the final rule specifies that this be based on human data, either published literature of human experience or other valid human studies. If there is no such human data, then the drug is considered to have pharmacological effect no matter how small the dose administered. The drug can, therefore, not be considered GRASE and is subject to IND submission.

So, what are the differences between conducting research under RDRC regulations or 361.1 versus an IND? The first major difference is in the allowed purpose of the research. Under 361.1 the purpose of the research is limited to basic research only, intended to obtain basic information

regarding the metabolism of the drug, such as kinetics or distribution, or to obtain basic information regarding human physiology, pathophysiology or biochemistry. The purpose of the research cannot be for immediate therapeutic, diagnostic or similar purposes, or to determine safety and effectiveness of a drug in humans for such purposes. A clinical trial cannot be carried out under 361.1.

Under IND regulations the purpose of the research is not restricted. IND research can include research involving therapeutic, diagnostic or preventive benefit to the subject; can involve the study of safety and efficacy as in a clinical trial; can include basic research that does not meet the requirements of 361.1; and even basic research that does the requirements of 361.1 can alternatively be studied under an IND.

Both RDRC and IND research require the review, approval and oversight of an institutional review board or IRB for the protection of the safety of human research subjects. The regulations

governing the function of an IRB are found in 21 CFR 56. Those responsibilities specifically include review of initial research and subsequent changes, and also the continuing review of ongoing research. The IRB has the authority to approve, require modification or disapprove research activities and can suspend or terminate approval of research.

The sponsors of INDs or RDRC investigators must obtain the approval of the IRB before any research can be initiated or any changes to the research can be implemented. The criteria for approval of a study by an IRB are listed on the slide. They include minimization of risk to subjects; equitable selection of subjects; and compliance with the 21 CFR 50 which includes the informed consent requirements, as well as additional safeguards for children in clinical investigations.

Beyond the role of the IRB, the oversight of RDRC and IND research differs. 361.1 provides for the formation of radioactive drug research

committees or RDRCs. These committees are approved and monitored by the FDA. It is the RDRC's responsibility to ensure that the requirements of 361.1 are met by a study both initially and as the study progresses. Specifically, the RDRC has to ensure that the purpose of the study is appropriate; that the dosing, which I will speak about in a couple of minutes, meets the regulations; that there are qualified study investigators; proper licensure for radioactive materials; appropriate selection and consent of research subjects; appropriate quality of radioactive drug administered; sound research protocol design so that information of scientific value is obtained from the study; appropriate reporting of adverse events; that there is approval of the study by the IRB; and that the labeling requirements of 361.1 are met.

In contrast, for IND research the FDA has a large role in the review and oversight of IND research. The FDA will review new protocols; protocol changes; the qualifications of study

investigators; chemistry, pharm/tox information, etc., with the primary objectives of assuring the safety and rights of subjects and assessing the scientific quality of the research.

For RDRC research, the FDA may never see such things as pharm/tox or chemistry information or even the protocols. Also, in contrast to RDRC research where the RDRC actually approves studies, the FDA does not approve studies under an IND; the FDA allows them to proceed. Only in the first 30 days after initial IND submission does the sponsor have to wait for FDA review before the study can be initiated. Following the first 30 days, the sponsor has to get IRB approval for any new research under the IND or any changes and has to notify the FDA but does not have to wait for FDA review.

The differences in the requirements for reporting to the FDA reflect the different role of the FDA in the oversight process. For research under 361.1 the reporting allows the FDA to monitor the activities of the approved committees. Under

IND regulations the reporting allows the FDA to monitor the safety of subjects and the quality of the research.

361.1 requires that an RDRC submit an annual report. The annual report consists of a summary of each study conducted under the RDRC during the previous year, such information as the title and description of the study, the number of study subjects and the radiation dose received by each subject. Also included in the annual report is the committee membership summary which is submitted annually, as well as any time during the year that there is a change in committee membership.

Special summaries are submitted at any time that an RDRC approves the use of more than 30 research subjects or the use of subjects less than 18 years of age. There are adverse event reporting requirements under 361.1 and, if specifically requested by the FDA, minutes of RDRC meetings and full protocols must also be submitted.

Annual reports are also required for IND

research but they include different information. They will include safety information, manufacturing changes, preclinical data, summary of study results, etc. The sponsors of INDs are also responsible for reporting new protocols, protocol changes, adverse events, etc.

In terms of FDA enforcement actions, the FDA will notify RDRCs when the requirements of the regulation are not met and when studies must be stopped. The FDA can also conduct on-site inspections and, if warranted, can withdraw the approval of the RDRC.

Similarly, for IND research the FDA will notify sponsors of deficiencies, can conduct on-site inspections and, if warranted, can put a study on full or partial clinical hold or can terminate the IND.

Under 361.1 there are limits to both the pharmacological dose and the radiation dose that can be administered to subjects. The pharmacological dose is limited outcome the amount of active ingredient known not to cause nay

clinically detectable pharmacological effect in humans, based on human data. The irradiation dose is limited to the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study. There are single radiation dose and annual and total radiation dose limits specified by the regulation for different organs.

In contrast, for IND research there are no limits to pharmacological or radiation dose. Those doses are evaluated on a case-by-case basis. Under IND, the initial pharmacological dose can be chosen based on either animal or human data.

The IRB regulations require that an IRB assure that there is compliance with 21 CFR 50 before it can approve a study, and 21 CFR 50 includes Subpart B, which are the informed consent for human subjects regulations, as well as Subpart D, the additional safeguards for children in clinical investigations. RDRC research must obtain IRB consent before it can proceed. Therefore, RDRC research is in compliance with 21 CFR 50, as is IND

research.

Under 361.1 the number of study subjects is limited to the number sufficient but no greater than necessary for the purpose of the study, and the number should reflect that the study is intended to obtain basic research information only. Generally, 30 subjects or less are sufficient for an RDRC study. However, if an RDRC approves a study for more than 30 subjects, then a special summary must be submitted to the FDA that includes a justification. There is no limit to the number of subjects for IND research.

The use of subjects less than 18 years of age is permitted by RDRC regulations but only in special situations, specifically, when it can be demonstrated that the study presents a unique opportunity to gain information not currently available; when the study requires the use of subjects less than 18; and when the study is without significant risk to the subject. Again, if the RDRC approves a study in subjects less than 18 years of age a special summary has to be submitted

to the FDA.

Women of childbearing potential must state in writing that they are not pregnant or be confirmed as not pregnant on the basis of a pregnancy test before they can participate in RDRC research.

Under an IND, the use of subjects less than 18 years of age, women of childbearing potential and even pregnant patient is permitted and is evaluated on a case-by-case basis.

Finally, there are adverse event reporting requirements for both RDRC and IND research but they do differ. RDRC regulations require the reporting of adverse events that are associated with the research study itself, whereas, IND regulations require that a sponsor report all information relevant to the safety of the drug regardless of the source.

Specifically, under 361.1 and investigator must immediately report to the RDRC all adverse events associated with use of the radioactive drug in the research study, and the regulation does not

define "immediately" but the FDA recommends that serious adverse events be reported within two business days and all others reported within five business days.

After the adverse events are reported to the RDRC, the RDRC must then immediately report to the FDA all adverse events probably attributable to use of the radioactive drug in the research study, and the FDA recommends that serious adverse events be reported within 7 business days and all others within 15 days.

Under IND regulations, a sponsor must review all of the infection relevant to the safety of the drug from any source, foreign or domestic. That includes the information from his or her own study, any other clinical trials, published or unpublished literature, animal studies, commercial marketing, etc. After review of this information, the sponsor has to submit safety reports of unexpected fatal or lief-threatening adverse events within 7 days of receipt of the information, and serious and unexpected adverse events within 15

days of receipt.

Lastly, the IND annual report also contains adverse event information, such things as a summary of the most common and most serious adverse events, and a list of patients who dies or who dropped out due to an adverse event during the previous year.

That concludes my summary and now Dr. Jerry Collins will speak regarding examples of appropriate RDRC study design.

RDRC: Examples of Appropriate Studies

DR. COLLINS: Good morning. The two general categories of studies that are appropriate for being conducted under RDRC, if the drugs meet the conditions Dr. Panholzer has just mentioned, are metabolism and excretion studies. You may have noticed on Dr. Mills' slide earlier a description of how frequently we see studies with carbon-14 or tritium. Almost in every case, what we are doing is looking at plasma, urine and feces to find out what transformation products there are and what routes of excretion drugs have. In general, that

is about 20 percent of the number of studies that are conducted under RDRC.

Imaging studies represent the other 80 percent, PET, SPECT, gamma, and members of this audience refer to such studies as noninvasive functional imaging or molecular imaging.

Again, for drugs that meet the conditions of 361.1, appropriate examples of imaging studies cover a wide range of categories--biodistribution, which organs or tissues in the body is the drug excluded from, which ones may it concentrate in. In the pathophysiological domain, such as the presence of a tumor, how does that change or alter the distribution. For things like receptor binding, transport processes, enzyme activity, imaging studies all have a role in providing basic research information in those categories. For more global assessments or multi-step processes, like DNA synthesis, cellular proliferation or apoptosis, again, there are active efforts under way at the RDRC level to obtain basic research information in these categories.

We hear a lot of interest from audiences such as these on the use of radioactive drugs as research tools. The ground rules for research tools are that there is no intent to develop the radioactive drug as a tool; it is just a waystation to gain information. Secondly, particularly if it is going to be used under the RDRC regulations, there is no intent to individually adjust patient therapy while the studies remain at the RDRC stage. Of course, response data can be collected and analyzed retrospectively. And, of course, if RDRC studies are promising you can decide to pursue further develop of the radioactive drug with an IND, or you may decide you have already learned what you needed and never have a use for that particular radioactive drug again.

It can be a challenge to work our way through the regulatory process when there is simultaneous use of a radioactive drug and a therapeutic drug. I think the easiest rule for understanding that is to evaluate the requirements for an IND separately in those cases. So, in the

first example, if we think that a radioactive drug meets the requirements of 361.1 then it is appropriate for the use of that radioactive drug to be approved by the RDRC. If it fails to meet the criteria, as described by Dr. Panholzer, then an IND is needed for the radioactive drug.

Looking separately at the therapeutic drug, the question here is the use of that therapeutic drug IND exempt. If that is true, then the IRB can approve the study. If it is not true, then and IND is required for the therapeutic drug.

Sometimes the radiolabeled drug and the therapeutic drug have completely different structures and so there will be completely separate INDs that are required. Sometimes they have the exact same chemical structure, except for a change in the isotopic composition, and in that case either separate INDs can be filed or they can be filed under the same IND. So, again, the operating rule is to evaluate the need for an IND for the radioactive drug piece separate from your evaluation of the need for an IND for the

therapeutic piece.

Let's look at a concrete example to see if this is clear. Studies done at Brookhaven National Laboratories more than ten years ago, by Johanna Fowler and Norah Volkow, looked at monoamine oxidase type B enzyme activity. The radioactive drug that they used, the so-called probe for enzyme activity, was the carbon-11 version of Selegiline. Selegiline was, and is, a marketed drug and so the RDRC is an appropriate venue for approving a study looking at carbon-11 Selegiline as a radioactive drug of enzyme activity. The baseline image that they obtained, and published ten years ago, is consistent with what we know from postmortem studies of the human brain. So, it appears to faithfully represent the phenotypic map of MAO-B activity in the brain.

When subjects were then given therapeutic doses of Selegiline and enzyme inhibition was examined, only 5 mg twice a day, which is the exact labeled and approved dose in the product labeling and reprinted in the PDR, essentially all of the

enzyme activity appears to be abolished, using carbon-11 Selegiline as the probe.

This study, even though it combines a radioactive drug and a therapeutic drug, is still within the bounds of the radioactive drug research committee because there is no need for an IND either for the therapeutic drug, which is a marketed drug, or for the radioactive probe.

The next year the same investigators kept the same radioactive drug, carbon-11 Selegiline, but changed the therapeutic drug to Lazabemide. Lazabemide has never been a marketed drug and has always been studied under an IND. So, the therapeutic piece of this study requires an IND for the use of Lazabemide. The radioactive drug, on the other hand, because it is a probe that is a radiolabeled version of a marketed drug, can be approved by the RDRC. Any findings from this study are required to be reported to the IND for Lazabemide but the approval of the radioactive drug studies itself can be done by the RDRC.

A frequent question that we get at the

agency is whether it is okay to add a radioisotope to a molecule that does not have the same atom in it. Yes, historically, the agency has accepted this interpretation as within the boundaries of the RDRC. Investigators and the RDRC have to be aware and consider the possibility, however, that the addition of a radioisotope, such as fluoride-18, may considerably distort the properties of the host molecule and in doing their scientific evaluation of the study should take that into consideration on a case-by-case basis.

So, we have been focusing on what is able to be done under current RDRC rules; what does that leave us for studies that can't be done? No first-in-human studies are permitted under current RDRC rules because there is a requirement to have human data that shows no pharmacological effect. Furthermore, as Dr. Panholzer mentioned, the regulations are very clear that no individual or immediate patient benefit is anticipated so it is not expected that RDRC studies would permit individual patient decision-making.

Earlier this year, the Commissioner of FDA announced an initiative called the Critical Path for Drug Development. In that Critical Path initiative, FDA has recognized the potential role for noninvasive imaging in the drug development process. FDA is working with the trade associations, BIO and PhRMA, with professional societies such as the Drug Information Association and academia to convene a workshop on the use of imaging in drug development, and we hope to have an announcement before early 2005.

In addition to this meeting today, FDA staff have been meeting with professional societies, such as the Society of Nuclear Medicine, to exchange views on the use of noninvasive imaging and interactions with the FDA.

We have also announced that we are considering a guidance document to simplify requirements for exploratory INDs, and we also have an inter-agency initiative with the National Cancer Institute and have formed three joint working groups to explore how the imaging process might be

considered in drug development.

In summary, the RDRC process has been, over the last 30 years, a successful mechanism for a large number of studies. If we consider the three molecules that are universally accepted as safe and effective, FDG, fluoride and ammonia, all three of those molecules could appropriately have their initial studies conducted under RDRC as long as the scope of those studies only covers basic research. After they proceed further into development the IND process is appropriate.

In addition, a survey of the literature and abstracts of the Society of Nuclear Medicine meetings, and so forth, would find a very large list of research conducted under the RDRC, or research appropriate to be conducted under the RDRC, in which the probes were essentially research tools. In some cases, such as for example the use of carbon-11-fluconazole or carbon-11-triamcinolone, the sponsor of those studies only had a very simple, basic question to answer. The study was done once and there was no

further use for that probe. Other studies, such as 15-oxygen-water, 18-fluorine-FLT, 18-fluorine-estrodial, represent probes that have multiple uses to answer different basic questions at different times, and many of those probes may well graduate to IND and full development stage. But at some point in their development they obtained useful information on basic research under the RDRC stage.

So, under current RDRC rules, what can be done? Well, certainly the limitation of the human imagination and 30 years of experience with RDRC, we have seen everything that was on the list for my second slide. We have seen biodistribution studies; receptor binding studies; imaging of DNA synthesis; and so forth. That is where we are today.

The next presentation will be by Dr. Sally Loewke, the Deputy Director of the Division of Medical Imaging and Radiopharmaceutical Products, who will discuss the concept of pharmacological effect.

RDRC: No Clinically Detectable
Pharmacological Effect

DR. LOEWKE: Good morning. As Jerry mentioned, I am here to introduce the topic of clinically detectable pharmacological effect and, in particular, what we mean when we say no clinically detectable pharmacological effect.

This topic obviously stems from the regulation 21 CFR 361.1(b)(2), limit on pharmacological dose, which states the amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.

Also under 21 CFR 361.1(d)(2), pharmacological dose states to determine the amount of active ingredients to be administered, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

The current regulation allows for the

administration of many types of radiolabeled drugs as long as they are known not to cause pharmacological effect in humans. Some of these types of drugs include radiolabeled endogenous compounds. These are normal body constituents and are generally considered safe. However, when produced in excess either by the body or exogenously administered, they may become harmful. Therefore, in order to use these types of products one must be aware of their daily production rates and normal levels to determine the potential effects of the additional amounts being administered.

Also allowed under RDRC are other radiolabeled drugs and radiolabeled biologics. One caveat to the biologics is that most biologics are known to cause an immunogenic response and, therefore, wouldn't necessarily meet the no pharmacological effect stipulation of the regulation. As Jerry mentioned, what the regulation does not apply to is first-in-human studies.

Two issues that I want to talk a little bit more about is, again, the issue of availability of existing human data. What this is essentially saying is that animal data alone is not sufficient to ensure the lack of pharmacological effect. Thus, first-in-human studies are not permitted.

I also briefly wanted to touch upon pediatrics and Dr. Goldkind will expand later. There may be difficulties when doing research in children, if you have known use in adults and extrapolating dose to kids, due to differences between adult and pediatric populations as listed on this slide. There are physiologic differences, organ/system maturational differences, hormonal differences, neurobehavioral differences, growth issues, all of which make arriving at a dose in pediatrics maybe a little bit more difficult.

The other issue is the lack of a definition for clinically detectable pharmacological effect. The regulation doesn't provide for one but, yet, we need to understand what clinically detectable pharmacological effect

is to be able to define what no clinically detectable pharmacological effect means.

So, to basically get the ball rolling and the discussion going, I have provided several types of events that could constitute a clinically detectable pharmacological effect, and that includes a subject reporting a symptom; an adverse event occurring; changes in baseline vital signs noted; changes in targeted monitoring. I just specified targeted monitoring because, dependent on where the drug localizes or how it might work, it may be a receptor binder. Mere vital signs might not be enough to assess the safety or the lack of pharmacological effect and you may need more involved monitoring, such as physical exam, ECG and other diagnosis tests. And, of course, the immune response.

Thus, we are here today to seek your input on what clinically detectable pharmacological effect means in the context of RDRC, and this would include what levels of administration of endogenous compounds are safe and what parameters are needed

to be monitored to ensure the lack of pharmacological effect for all products administered under RDRC.

The next speaker will be Dr. Orhan Suleiman, speaking about radiation dose limits.

RDRC Radiation Dose Limits

DR. SULEIMAN: Good morning. I would like to make a note for the record, I am a Fellow in the American Association of Physics and Medicine. Those of you who got the agenda have me listed as a Fellow in the American College of Nuclear Physicians, and my apologies to the American College of Nuclear Physicians. We figured it was better to save some paper and just make that statement up front.

I will be discussing radiation dose limits. I guess the first question is whey do we need to revisit the dose limits. Well, first, in 1975, when we adopted these dose limits, they were actually the Nuclear Regulatory Commission's occupational dose limits. During the intervening period of time, we have seen evolving radiation

metrics. We have seen some new concepts introduced, effective dose for assessing risk. We have seen new data and we have also seen new regulations regarding human research.

These are the current limits established in '75 when we adopted the Nuclear Regulatory Commission's then occupational dose limits. We set limits for a single and an annual dose limit and we, de facto, established a two-tier set of standards, one for the whole body, the other that was organ specific.

We further reduced the dose for research subjects under the age of 18 to 10 percent of the adult dose, fully aware that they may be at increased risk for radiation carcinogenesis.

We also required that these limits apply to x-ray exams associated with the research study since the body does not differentiate between the source of the radiation.

The rationale for using occupational dose limits at that time was, like the occupational worker who knows that his or her work has increased

risk, the human volunteer makes an informed decision. And, even though there was concern that the whole body limits were of concern, the belief that the radiation dose would be as low as reasonably achievable justified this practice. I believe one of the values of the RDRC experience is that the actual doses must be determined. After all, how can one know that they are giving as low as reasonably achievable if one doesn't even know the dose that the subject is receiving?

A review of the RDRC annual reports further shows that organ doses have, in fact, been the dose constraint in research studies, not the whole body dose limit, and that RDRCs are generally in compliance with these dose limits, not necessarily surprising since this is self-reporting, but encouraging nevertheless.

I originally labeled this slide as confusion but I think one of the first steps in solving the problem is identifying it and in the last year and a half, since I have been associated with the program, it has been obvious that the

confusion that the radiology community has dealt with over the last 30 years has been shown in this program as well. In 1975, when we adopted the dose limits, the dose equivalent unit was the rem. Two years later, the International Commission on Radiological Protection promulgated effective dose equivalent, H. During this period of time we had the march toward standardization using the SI standard international system of units, rads to Grays, rems to Sieverts, mCi to megaBq. Unfortunately, even today there is quite a bit of inconsistency in how people report radiation units.

In 1991, the Nuclear Regulatory Commission adopted effective dose equivalent for their dose limits. During the same period of time the ICRP replaced effective dose equivalent with effective dose--similar in concept, but there are differences. Two years later, the National Council on Radiation Protection adopted or came out with effective dose for the U.S. In 2004, the ICRP is now modifying or proposing a modification of effective dose.

I give this to you just to clarify that there are reasons for the confusion. I don't intend for this to be a primer on effective dose but basically effective dose is a homogenized single metric for radiation risk. It equates partial body irradiations with a uniform whole body dose. This was designed as a unit of radiation protection, not intended for scientific studies or epidemiological studies where the specific organ doses need to be known, along with the age and the sex. To calculate effective dose one simply multiplies the dose to a specific organ times its tissue weighting factor and simply sums all these up.

Here are the original 1977 tissue weighting factors, the current and the proposed tissue weighting factors. As you can see, these have changed with time and unless one understands how this is calculated, an individual organ can receive an exceptionally high dose. The sum of all the tissue weighting factors must equal one. So, when the tissue weighting factors are modified some

have to be given more weight, some have to be given less, sort of like congressional reapportionment periodically.

So, as a radiation metric for dose limits it is all right. There are some limitations but the inherent value of using effective dose is that it allows you to compare radiation dose from a variety of sources, and I think this is the very important characteristic of effective dose. Using effective dose for standardization, looking at column two where we have calculated effective dose from a variety of sources, we can compare the relative risk from some other metrics, such as the standard chest x-ray, column three; background time, column four; and the risk of lifetime cancer mortality, column five. When I show this to different people, it is interesting to see which one different people seem to relate to.

These are average doses but inherent in these numbers is a certain amount of variation. Background environmental doses may vary by a factor of two or more, depending on where you live and so

forth. Radiopharmaceutical doses may vary by several factors, depending on the administered dose and the body size. And, x-ray doses can vary by as much as an order of magnitude, based on many variables which I really don't have time to discuss here.

The bottom two lines show the RDRC whole body limit, and I have selected the red bone marrow limit for calculating effective dose. One observes that the organ dose is much more limiting and actually introduces a much higher level of safety.

Therefore, are 29-year old dose limits still appropriate? If not, what does limits would be appropriate? And, should we consider age specific dose limits?

Now, in effect, we did recognize that subjects under 18 were at a higher risk so we did introduce a factor of 10 lowered dose, but we have repeated this exercise here for pediatric doses. Again, the bottom two lines show that current pediatric dose limits are 10 percent of the adult limits and the relative risks. Again, I want to

emphasize that we have observed few, if any, pediatric studies under RDRC oversight and, second, the constraining limits are the organ dose limits, not the whole body dose limits.

I also want to make an important point, properly administered nuclear medicine exams and filmed-based x-ray exams should give a lower dose to smaller subjects. This is because the smaller size requires less administered radiation. However, as an aside but very relevant, electronic imaging such as computer tomography or filmless digital x-ray exam can deliver very high doses to children if adult techniques are used. So, inherent in all of this is that the radiation dose administered in terms of radioactivity should be known, and that the calculated organ dose and effective doses should be known. So, these are the risks expressed in a variety of ways.

There has been much change since '75. We now have new human research regulations which may require recalibration of these standards. We also know that the younger subjects are at increased

risk. We know that there are non-cancerous risks associated with radiation, specifically heart disease, digestive diseases and respiratory diseases, and that this is still a work in progress, with more of this data becoming available in the near future.

I want to thank Dave Preston for providing me with this slide, but here are some of the most recent data, again, showing increased risk for the younger survivors of the atomic bomb, specifically the 0-9 age group at exposure who are now 59-69 years of age; and the 10-19, 20-39 and over 40 age groups. So, we have new science. We have new rules. And the next speaker, Dr. Sara Goldkind, a bioethicist, will be discussing pediatric research regulations and their impact on 361.1.

But the questions we ask again are do current dose limits for pediatric subject pose a significant risk? If not, what dose limits would be appropriate? And, should there be different dose limits for different age groups? Thank you.

Pediatric Studies Under an RDRC

DR. GOLDKIND: Before I begin I would like to ask the audience a couple of questions. I would like, by a show of hands, to find out who here is an RDRC member or chair. How many of you actually review and approve pediatric studies under your RDRC 361.1? And, do the RDRC chairs and members have a policy? We have heard that there are some RDRCs that have a policy that they will not review pediatric studies under this regulation. Could I have a show of hands of those that will not?

I am going to pull together a few strains that you have already heard and try and give our thinking about pediatric studies and RDRC. In order to do that, I would like to start by looking at adult studies briefly. Then I am going to look at pediatric studies and discuss the Children's Health Act, 21 CFR 50, Subpart D, which is additional safeguards for children, and the current understanding of risk levels that we find in the HRPAC report and in the IOM report, and what we consider to be additional risks for the pediatric population.

The research subjects shall be at least 18 years of age and legally competent. So, looking at adult studies first, we have the algorithm that we have to understand does the study meet 21 CFR 361.1? If it does, then no IND is required and the research can go forward under the 361.1 and RDRC approval. If it does not meet the stipulations of 361.1, then an IND would be required if the research is going to go forward.

Some of the conditions that are necessary for RDRC approval are the limit of the pharmacological dose. We have heard that there has to known not to cause any clinically detectable pharmacological effect in human beings based on available data from published literature or from other valid human studies. This is a challenge that we have to face looking at pediatric studies.

There has to be a limit to the radiation dose. There has to be the smallest radiation dose with which it is practical to perform the study. Single dose and cumulative dose limits are important. And, RDRC approval requires IRB

approval and, in order to have IRB approval, there has to be compliance with 21 CFR 56, which are IRB regulations, and IRB regulations require compliance with 21 CFR 50, which encompasses informed consent and Subpart D.

So, now looking at the algorithm for pediatric studies, 361.1 does permit currently pediatric studies. They are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not currently available, and the study requires the use of research subjects less than 18 years of age, and is without significant risk to the subject.

So, putting 361.1 into a historical context, this regulation was passed in 1975 and at that time the phrase that was used was without significant risk to the subject, which is not defined. Since then, we had tremendous protection of children and little pediatric research. But in the 1990s there was a growing awareness that children were treated on the basis of sparse

pediatric data and extrapolations from adult data. In 1997 the Food and Drug Modernization Act allowed for product exclusivity with a marked increase in pediatric research and, to date we have had over 40,000 children included in studies generated by pediatric exclusivity. In 2000, the Children's Health Act was legislated and it states that all HHS funded and regulated research must comply with these additional protections for children. In 2001, the FDA adopted 21 CFR 50, Subpart D. Subpart D does not talk about without significant risk. It talks about minimal risk and greater than minimal risk.

Now, how is it that Subpart D is applied to research conducted under 21 CFR 361.1? In 21 CFR 361(d)(5) it states that each investigator shall obtain an IRB review that conforms to 21 CFR 56, and 21 CFR 56.109(h) states that when some or all of the subjects in a study are children an IRB must determine that the research study is in compliance with part 50, Subpart D.

So, what does Subpart D say? Subpart D

divides studies into four categories. The first two categories are 50.51 and 50.52 and there are four critical concepts to Subpart D. The risk assessment is one. Whether or not there is direct benefit to the subject is another. Whether or not the benefit is to a class of children with a similar disorder or condition is yet another. So, disorder or condition is a critical concept to understanding how to categorize under Subpart D.

So, 50.51 states that the risk is basically minimal to the subject. 50.52 states that it involves greater than minimal risk but presents the prospect of direct benefit to individual subjects. So, radiation exposure prohibits classification under 50.51; it is greater than minimal risk. Basic research under 361.1 cannot be classified under 50.52 because, by definition, there is no direct benefit.

So, the two categories under Subpart D that would be conceivable to classify pediatric research for the purposes of studying under RDRC would be 50.53 and 50.54. 50.53 states that the

research involves greater than minimal risk and no prospect of direct benefit to the individual subjects involved, but likely to yield generalizable knowledge about the subjects' disorder or condition and 50.54 states that the IRB could not otherwise approve the research under one of the first three categories.

So, under 50.51, 52 or 53 the IRB outright has the authority to classify the research under one of those three categories. But if the IRB finds that it cannot classify the research under one of those first three categories, there is still a mechanism by which the research can be approved but it requires that that protocol be submitted to the FDA, if it is an FDA-regulated product. If it is federally supported or conducted research, it will also require that the protocol be submitted to OHRP. Under 50.54, an expert panel would be involved in reviewing that protocol and making the determination as to whether or not the research could go forward before we could go back to the question of whether or not it meets 361.1 criteria.

As I said, under 21 CFR 50.53 an IRB is authorized to make the approval. Under 21 CFR 50.54 the IRB finds and comments that the clinical investigation does, indeed, present an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children, and this requires FDA referral and HHS referral if the research is also federally funded and conducted.

It also requires review by an expert panel and the findings would then have to be sent to the Commissioner for final determination on the protocol, and the Secretary if it would also be referred to OHRP.

We will come back and revisit this algorithm a second time but let's look at a pediatric study. So, the first question that we think needs to be addressed is what are the findings that the IRB makes regarding CFR 50, Subpart D. If the IRB finds that the study does not meet those additional pediatric protections, then you are off on the right-hand side of the

slide and you cannot do the study. If the IRB finds that maybe it can approve the study under 50.54, then, as I said, it would have to meet the requirements that we just discussed and be referred for an expert panel review. Then, if the IRB feels that it does meet Subpart D, then under one of the other categories, not 50.54, likely 50.53, you go to the next question, does it meet the rest of 21 CFR 361.1, and we will come back to that question in a minute.

So, just to give a quick primer on how we understand risk right now, pediatric risk, minimal risk is defined in our regulations as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

What we see in this definition of minimal risk is a very low ceiling on the exposure we allow children to undergo, particularly health children or children who will not have any direct benefit to

the research.

Minimal risk examples, if you look at the preamble to Subpart D, some of the examples that are given in that document are clean-catch urinalysis, stood samples, EEG, minimal diet or daily routine changes, standard psychological test, taste tests, device test of oral temperature readings. NHRPAC is the National Human Research Protection Advisory Committee that is the predecessor to the current Secretary's advisory committee and it issues a report, which is available on the web, that venipuncture, chest x-ray, bone density test, oral glucose tolerance test, and MRI without sedation are examples of minimal risk. The NHRPAC report was neither endorsed nor refuted by OHRP. I do also want to mention, under venipuncture, that there is a caveat that we need to know the quantity and frequency before classifying it as a minimal risk procedure.

Greater than minimal risk is not defined in the regulations. However, the NHRPAC report suggests that urine collection via a catheter,

lumbar puncture, skin punch biopsy with topical anesthesia, bone marrow aspirate with topical anesthesia, and nasogastric tube insertion are examples of greater than minimal risk. The Institute of Medicine issued a very comprehensive report, back in March of 2004, which stated that it interprets greater than minimal risk to mean a slight increase in the potential for harm and discomfort over minimal risk.

A risk assessment requires that magnitude, probability, duration are all taken into account, that it be based upon age as well, and that there be both a cumulative analysis of risk as well as a component analysis of risk, and I will describe that in a moment, and that the inclusion of special populations with particular health concerns also be considered when we look at risk assessment.

So, if you look at a very low birth weight premature baby, that is going to be a very different risk assessment, or venipuncture in an anemic child will be a very different risk assessment than if you are looking at a healthy

child of an older age.

Component risk analysis means that you look at each intervention in the protocol. That we be radioactive drug risk; concomitant medications risks; radiation risk of the imaging machine; venipuncture, looking at the frequency of venipuncture and the total blood volume withdrawn; use of enclosed or confining equipment risks; risks of prolonged immobilization; use of sedation; and any additional protocol interventions all need to be taken into account. I have highlighted use of sedation because we feel that any time sedation is used that is greater than minimal risk.

So, now going back to the left-hand side of this flow chart, we have to ask the question, understanding better how we calculate risk, can we meet 21 CFR 361.1? If we can, indeed, meet it then no IND will be required. However, we have concerns that it will be very difficult to meet it. If, indeed, you cannot meet 21 CFR 361.1, then in order to do the research the IND would be required.

So, our concerns about meeting 361.1 for

pediatrics is that the amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect. That has to be based on published literature, as you have heard, or other valid human studies, and what we need to ask is how much of that data is really available for pediatric risk assessment.

We think there is a limited amount of pediatric data, and our experience with pediatric exclusivity has demonstrated repeatedly difficulties in extrapolation from adults to children based on differences in growth, development, absorption, distribution, metabolism and other hormonal factors.

You have heard the advantages of an IND discussed by Dr. Panholzer and so, in summary, we assess that pediatric studies have additional risks involved. They are involving a vulnerable population and that population warrants additional safeguards. And, we propose and recommend that pediatric research, therefore, be conducted under

IND. Thank you.

DR. MILLS: This concludes the FDA presentations we have for this morning. We are going to take a 20-minute break at this time. Remember, the facilities are out the door; that if you want to leave the building you are going to have to surrender that badge and sign back in; there is a telephone upstairs. And, not a cell phone went off during the entire morning session--congratulations! Those of you who are going to speak, that have scheduled times, we would like you to come up to the podium now so we can organize ourselves to have the morning presentations. There will be an open microphone and, again, the morning session will conclude this morning at 11:15. Thank you.

[Brief recess]

DR. MILLS: We are back from break. Thank you. We are now going to have the scheduled public speakers. Their slides are not at the back table but they will be posted on the meeting web site, and we will have that posting for you up at the

back table so you will know what the web address is for all of these slides that will be presented in the forthcoming session this morning, as well as in the afternoon session.

A little bit of orientation, there is a pointer up here if you need it. It will be on your left. Now we will have our first speaker, Dr. Mathew Thakur.

Public Presentations

DR. THAKUR: Thank you and good morning. My name is Mathew Thakur. I am a radiochemist by training and profession. My academic titles are Professor of Radiology, Professor of Diagnostic Oncology, and Director of Radiopharmaceutical Research at Thomas Jefferson University in Philadelphia .

This morning I am going to make brief remarks as the President of the Society of Nuclear Medicine on pharmacologic aspects of radiopharmaceuticals. These remarks are based upon our experience in which we administer millions of radiopharmaceuticals for diagnostic imaging. We

believe that most radiopharmaceuticals are prepared in high specific activity, which means we have effectivity for most of the time with micromole quantity of a substrate. Since we inject only millicurie quantities of the radioactivity, we inject only a picogram or nanomole quantity of the substrate. It is because of that reason that they do not activate detectable pharmacological effect.

Most diagnostic radiopharmaceuticals only slightly modify analogs of existing compounds. The toxicology of these compounds, when administered in large quantities, is generally known. Based on our experience, we believe that most radiopharmaceuticals, that is diagnostic radiopharmaceuticals, are administered only once. Most diagnostic radiopharmaceutical probes do not saturate targeted receptor molecules in the body, meaning that when we administer a small quantity of receptor specific compounds, they do not saturate the receptor pools that exist in the body. As a result, they do not induce any detectable pharmacologic effect.

Most diagnostic radiopharmaceutical probes have rapid blood clearance. As a result, they never produce equilibrium between the probe and the target molecule. As a result, again, they do not induce detectable pharmacologic effect. Therefore, we believe that the preclinical pharmacological data can be obtained in animal species. Blood clearance and distribution can be achieved or obtained, studied. Blood chemistry for renal, cardiac and hepatic function can be examined, and these data are presented to the RDRC. Investigators should then report if there is any significant adverse event to the RDRC and IRB, institutional review board.

What the RDRC and IRB should supervise are Phase I and Phase II clinical studies. RDRC will provide the summary of all clinical data, including any adverse events, to FDA and then investigators should file an IND at the end of those Phase I and Phase II studies. Those are all my remarks.

DR. MILLS: Thank you, Dr. Thakur. Dr. Eric Hall is our next speaker.

DR. HALL: The poet described time as an ever-flowing stream and that is the justification, I think, for suggesting that we have to look again at the dose limits allowed for studies under the RDRC because time has changed and a lot of things have happened in the last 30 years.

The present limits date from the 1970s. Several things have happened. In particular, the BEIR and UNSCEAR committees have revised their cancer risk estimates, revised them upwards. I don't have any inside information but the are likely to go up again.

Next, the ICRP has introduced the effective dose concept and, in particular tissue weighting factors. It has been pointed out that different tissues have got different risks for carcinogenesis.

Thirdly or fourthly, the NCRP reduced the dose limits for occupational exposure, and it is occupational exposure that the RDRC limits were based on back in the 1970s. I am not sure that there is any real justification for that, except to

try to limit, I suppose, the risks of exposure to something reasonable compared with other risks in life.

The NCRP recommends for occupational exposure a cumulative limit of 1 rem or 10 milliSieverts per year. That is the cumulative limit. You are allowed to have 5 rems or 50 milliSieverts in any one year for a limited period but not for a steady diet--for a steady diet, only 1 rem per year. NCRP doesn't have this dichotomy of what you are allowed in any one particular year. They allow an average of 1 rem a year. So, keep that in mind.

Now, the current limits you have already heard about. I have simplified them greatly. A single dose of 3 or 5 rem for certain organs, whole body, blood forming organs. And, I would submit to you that this makes absolutely no sense at all. This is a relic of the thinking of the 1970s. It doesn't make any sense to have the same limit for whole the body as it does for a specific organ because specific organ weighting factors are around

0.1. So, that makes no sense for a start.

The next thing that doesn't make any sense is to single out the ocular lens. Damage to the lens is a deterministic effect which a huge threshold of something like 2 Gray. So, we hope we never get to 2 Gray in any research subjects so that makes no sense.

Next, to single out the blood forming organs again is a relic of the thinking of the 1970s, at which time the only malignancy that was important in the Japanese survivors was leukemia. We thought that was the whole ball game. All of the solid cancers have come up later. So, the thinking from the 1970s is out of date. Time has, indeed, flowed on and we need to think again.

Now, I would like to simplify things rather than make them more complicated, and I would say that to the accuracy that we know Wt, the tissue weighting factor, we could assume that all radiogenic organs are about the same and ascribe Wt of 0.1. Now, in the current ICRP scheme, they vary from 0.05 to 0.12.

I think it is a bit of a joke to think that we really know the differences that accurately, and the current value for the gonads is big and that is obviously out of date because the proposed figures from ICRP for 2004 reduce the gonads particularly. It was big and we know now, with increasing evidence and research, that the hereditary effects of radiation go down and down in importance and now it is way down to 0.05 so we can forget that as a very sensitive indicator. So, I would suggest that in this simple system, if say they are all about 0.1, that would be near enough.

So, a proposed simplified system would be, say, for whole body to be 1 rem or 0.01 Sievert. For an individual organ it can be bigger by a factor of 10 because the tissue weighting factor is about 0.1, giving a total possible equivalent to what the ICRP recommends of about 2 per year. That would greatly simplify the whole system and, perhaps more importantly, bring it into line with current thinking and current evidence.

Now, that is all for the adult. Then,

when we think about the effect with age, these are the ICRP figures, revised slightly more recently from the Japanese data, which show that as the Japanese data mature one of the more striking features is the incredible variation of risk with age. So, although we take an average figure of 5 percent per Sievert as the cancer risk, it is almost a meaningless number because it is average. If you are a small child it is 10-15 percent per Sievert and if you are a mature adult it is barely 1 percent per Sievert. With such a dramatic variation with age, it seems to me that it would make sense to make two divisions rather than one division. To change at 18 really doesn't take into account this enormous change early on and, therefore, it might make sense to have 0-5 years, very sensitive, very young which appears so from the Japanese data, and then 6-18 years as an intermediate range, and then adult afterwards. That would seem to be justified.

I would just like to point out that is not an arbitrary definition. That is a piece of solid

human data, that the variation with age is very dramatic. At that point, I thank you for your attention.

DR. MILLS: Dr. Hall, thank you. Dr. Wayne Thompson is our next speaker.

DR. THOMPSON: Good morning. I am a medical physicist, Professor of Radiology at University of Tennessee Graduate School of Medicine. I am here to promote--and I think I get the sense other speakers have already thought about it--the jump from the current term whole body or total body radiation to something that is more current.

As was mentioned, the levels for RDRC restrictions breakdown to two categories, a lower set of doses allowed for more sensitive organs--blood forming organs, gonads--and a higher level of absorbed dose allowed for less sensitive organs. In reality, we do not expect any deterministic effects to tissue from these dose levels and what most concerns us is the stochastic effects of cancer induction and serious hereditary

defects. That is probably best reflected by the whole body limit to radiation.

The whole body radiation is an old term that we would like to get away from. I am going to talk about two other steps in dosimetry. Just historically, whole body/total body dose is the first that has been used by the RDRC, the current one. Those come from different historical origins but they are used interchangeably even by the same group. The really large step came in effective dose equivalent and then a significant but not as large conceptual change came in effective dose.

Whole body or total body dose was used by ICRP very early. I can trace it back to 1959. The Society of Nuclear Medicine did a lot of work in internal dosimetry computer modeling and used those terms in 1968, and those terms were around for the RDRC to adopt.

It makes two rather questionable assumptions based upon today's science, namely, it assumes first that it is uniformly distributed through all the body organs. In other words, if it

was uptake only in my head and maybe there were just short-term particles being emitted, it still assumed that the energy was absorbed uniformly all the way throughout my body. So, it wasn't very logical. It is almost never true. Tritium, yes; cesium-137, maybe.

The second weakness, in today's science, is that it does not recognize the limits that are imposed in terms of lower limits for sensitive tissues in terms of an organ tissue sensitivity component of this while body or total body dose. In other words, it is not a weighted average, weighted for tissue sensitivity. But at the time there was nothing better.

The major step came in 1977. The RDRC adopted a new concept called effective dose equivalent. They decided that, hey, let's pick out six sensitive organs. The gonads carry the hereditary defects; they were the most sensitive at that time. The least sensitive in that list of six was 0.03 and in between were breast, thyroid, red marrow and lungs. Then the way of computing a

single number--and this has been mentioned--was to take the dose to each organ, the six weighted, multiply by its sensitivity weighting factor, add that together and this would come up with a single number that reflected risk to an occupationally exposed patient at this time.

NRC is usually very conservative. Many years later it adopted that as making a whole lot more sense than the total body or whole body dose concept. In 1991 the second significant change, ICRP decided, you know, those weighting factors and everything, those really aren't right. We think now that there are 12 sensitive tissues instead of 6. Furthermore, the weighting factors used are based upon occupational exposure. It was predominated by males, with very little female component. It had things like inhalation, ingestion, all really occupation exposed concerns. It decided to change that to new weighting factors based upon general population, i.e., an equal number of males, an equal number of females and other concerns.

Today the effective dose is widely recognized, and really has been for years, as the most accurate measure of total potential detriment or total harm from what? From fatal and non-fatal cancer induction; from serious hereditary defects; and from life-shortening effects from both of those, from these stochastic effects of radiation exposure.

It made a statement in 1999, saying the effective dose can also be used to provide a relative index of harm for various procedures in diagnostic radiology and nuclear medicine. Those are key because we have to add the dose from the injected pharmaceutical to the dose of whatever x-ray, PET, CT scan or whatever else we are doing.

The ICRP then publishes tables of effective dose of new radiopharmaceuticals and the Society of Nuclear Medicine put its MIRD technique into software. I think largely the work of Michael Staven, and that was available to anyone. It was called MIRDOSE. That was recently replaced by OLINDA, which was FDA approved this year. And, put

in the hands of the investigators a tool to calculate effective dose for just about anything. There is a database of 850 radionuclides and you can imagine any one of those can be labeled to any pharmaceutical so it really leaves little left to do.

ICRP tables also list effective dose separately for adults, children or males and females. You would think this would allow some risk matching to subject body, and it kind of does, but you must remember that the weighting factors, tissue weighting factors are still the age and sex average so you can't truly use it to separate these groups out the way you would rally like to.

I did a poll about three months ago at various institutions. I went on-line and looked up their on-campus patient consent forms. I find that a great number of them are using effective dose for research guide limits. The NIH, and I have been in discussion with them on this for a while, has a brochure out entitled "Introduction to Radiation for NIH Research Subjects" and they promote the use

of effective dose as a guideline, and they require the calculation of effective dose for all research studies. Now, these two groups here, of course, are stuck when it comes to RDRC controlled compounds because we are not allowed to do that. So, we maintain a two-tier system and trying to add an x-ray dose to a radiopharmaceutical dose when there are no, that I know of, modern total body dose x-ray tables is kind of a challenge, and leads one open to having to come up with some means of doing that.

So, there are really three choices. One can stick with the whole body dose, total body dose. It is very outdated and very oversimplified. The fact that it considers a radionuclide which could be all concentrated in one critical organ to be, instead, uniformly distributed throughout, or at least the absorbed energy, leads to underestimates of this average body dose by a factor of 100. In fact, one paper I have says 160 underestimate because it assumes it is not all in the thyroid, or wherever it might be. Now, these

really high underestimates are probably more for iodine in the thyroid gland. Technetium, probably a factor of 2; other compounds a factor of 10. But still a lot of underestimates because a lot of the stuff that may be concentrated in a critical organ, they assume, could be uniformly everywhere else.

The effective dose equivalent would be a big step in the right direction. That was a major breakthrough in concept. It is required for NRC occupational dose but really it is probably not appropriate for research because our subjects are not inhaling and ingesting, and just males, or whatever.

The best way to quantitate risk is effective dose. It is the most accurate for true risk estimates and it is the way. There are tables in the literature for effective doses for all common x-ray exams, and there are means to calculate effective doses for all radionuclides in the hands of the users or researchers. So, that is really the only practical way to combine those two.

I will close by saying that the ICRP

draft, if you look up the ICRP draft 2005 on your search engine, you will find it there. It is out there and for comment until the end of December. It makes a statement in the body of the paper that there should be one term to encompass the idea of risk, and that term is effective dose. Thank you.

DR. MILLS: Thank you, Dr. Thompson. Our next speaker will be Dr. Henry Royal.

DR. ROYAL: Thank you very much. I wanted to share with you some of the things that I have done in the past. One thing that I wanted to highlight is that I was on the Presidential Advisory Committee for Human Radiation Experiments. We spent about two years talking about radiation risk and the ethics of doing experiments involving radiation. I wish I could tell you that that gave me very clear insight into what we should be doing and, I must say, what I have learned is it is a very complicated issue and there are a lot of factors that need to be considered, and I hope to share some of those with you.

What I thought I would do is just briefly

talk about the current regulations since other speakers have addressed them; talk about what their limitations are; talk about communicating risk because it is hard to formulate regulations unless we understand the risk ourselves; and then answer the questions which the FDA asked us to answer, and make a few other comments.

So, you have already seen this. I am not going to spend any time of it, what the current limitations are in terms of dose. One of the things that I think is a problem with the current dose limits is, number one, they are linked to occupational exposure. Number two, they are based on whole body dose. There is no adjustment for age and there is no adjustment for life expectancy, and I will talk about each of these one at a time.

The linkage to occupational exposure is unclear to me. The rationale was unclear to me. Obviously, with occupational exposure the chance that this is going to be year after year exposure with research subjects it would be very unusual that a research subject would participate in

research involving radiation exposure year after year.

One of the statements that you heard is that the risk involved in an RDRC study should be minimal. One of the real problems, however, is the ambiguity of the definition of minimal risk. And, one of the things I hope to convey when I talk about risk communication is that the risk from radiation is perceived very differently depending on how you frame that risk. I don't know the right way to frame that risk, but I do know that how you express the risk has a great impact on how people perceive that risk.

In terms of whole body dose--so, the current regulations depend on whole body dose and I think everyone has commented that this is no longer the appropriate way to express the radiation dose and it should be replaced by the effective dose.

One thing I would like to highlight is that the dose is really a surrogate for what we would like to know, and that is the risk of the study, but it is not a very good surrogate for risk

because it has not been modified to adjust for age and to adjust for life expectancy.

This slide is very much like the slide that Eric showed you, just indicating that risk from radiation exposure does vary quite a bit based on age. However, the current regulations have a 10-fold factor built into them and a more appropriate factor might be a 3-fold factor.

The reason life expectancy is very important is because of the fact that there is a latent period between the time you have your radiation exposure and the time that a measurable increase in cancer incidence occurs and, therefore, someone who has a limited life expectancy is unlikely to experience the adverse consequence of having been exposed to radiation.

In terms of communicating risk, as I have mentioned, the magnitude of risk really depends on how you frame it. The common approach that you heard practically by all speakers today is in terms of how it increases the risk of having a fatal cancer. I can tell you that if you tell any

patient that there is a chance that you may die from participating in this activity most of them are not going to think very positively about participating.

So, using the common way of expressing risk for a 5 rem ED one might say that participating in a research study will increase your chance of getting cancer or of dying by 2/1000. The problem with this approach is that it is very difficult for most people to think in terms of numerical risk. It doesn't distinguish between dying today versus dying sometime in the future. Again, it does not account for age or life expectancy. Certainly, one of the things I hope we can all agree on is that there is a difference between dying today and dying 20 years from now.

So, an alternative approach is to talk about days of life lost, and the ICRP actually uses this concept. If you express radiation risk in terms of days of life lost, if you have 2/1000 times chance of dying and that death causes your life to be shortened by 15 years, then that would

result in an 11-day loss of life. One of the reasons why you might want to convert to days of loss of life is that you can then compare that risk to other risk.

To show you that this calculation is not totally off the wall, if you look at the survival curves for the Hiroshima and Nagasaki survivors, this is a zero dose population, and the dotted line, here, is also a zero dose population, and this green line is less than 25 rem exposure. You can see that it is very difficult to tell a difference in survival among this population. I certainly believe that it is pertinent to avoid radiation exposure but I think the point of this slide is to show that the risk is small and difficult to measure. In this article, they gave some numbers in terms of life shortening for various doses.

If you go to the loss of life expectancy, you can then compare the loss of life expectancy with other every-day risk. So, there is a reference here that you might want to look at to

see how they calculated it. There are all kinds of problems with these sorts of comparisons also, but it certainly illustrates the point that framing of the risk changes people's perception of it. I am not sure of the right way to do it, but I can tell you that framing it in terms of this is going to increase your chances of dying also has a big effect on how it is perceived.

Another alternative might be to compare it to background risk. We are all exposed to 100 mg of radiation every year of our lives so over our lifetime we are exposed to 7 rem of radiation. It is not possible to measure risk related to variations in background radiation and certainly these variations within the same kinds of doses that we are talking about our RDRC studies.

One of the things that no one has talked about that I think is a very important topic is unintended consequences. Dr. Suleiman mentioned that having organs as our dose limit is really the constraining variable and that makes doing RDRC studies safer. But I think when you look at safety

you have to look at the risk of the radiation exposure and the risk of not doing the research and the risk, therefore, of not benefitting from the research. So, it is not clear to me that overestimating the risk necessarily makes you safer.

The other thing that I wanted to illustrate is the problem of collective dose and what would happen if you lowered the radiation limit. A common kind of study that is done is an activation study, for example in the brain, and if you study more subjects because you are constrained by the radiation dose, you have to actually study more subjects so your collective dose is bigger because now you have to control for inter-subject variation. So, it is much better if you are doing some types of studies to be able to do the study in the same individual. If you do increase the collective dose, you certainly could argue that the total number of people who are harmed increases even though you have imposed this lower radiation safety limit.

Then the last thing is opportunity cost. Any time we make the cost of doing the research study greater, it means that those funds are no longer available to do other things which would protect the public's health.

So, in terms of the answers to the questions, as I said, the 5 rem annual dose was picked because of occupational exposure. I don't know that I could really logically justify that but I think that that is about the right level for a dose limit. But we should be adjusting for age and life expectancy so dose would be a better surrogate for risk.

I would recommend not paying much attention to organ doses. They are already accounted for in terms of stochastic effects when you use effective dose, and they should only be limited out of concern for deterministic effects.

We certainly want to keep the regulations simple, and that is sort of hard to do because radiation exposure and pharmacology are complicated, and we want to avoid unintended

consequences. Thank you.

DR. MILLS: Thank you, Dr. Royal. Our next speaker is Dr. Michael Gelfand.

DR. GELFAND: I am the past president, once removed, of the Society of Nuclear Medicine and I am also the past president of Pediatric Imaging Council, and my practice is pediatric nuclear medicine.

First of all, I just want to mention that nuclear medicine is widely used in children's hospitals. These are the procedure volumes from three of the biggest children's hospitals for 2003. So, pediatric nuclear medicine is alive and well and is expanding in its utilization.

At my hospital in Cincinnati, Children's, we have experienced continued growth in nuclear medicine volumes, at a little bit slower rate than the total number of exams, and we have been increasing in nuclear medicine at 1-5 percent a year, whereas radiology has been increasing at about 7.5 percent per year. It is also a growing population in the area.

We mostly GU studies. We do some bone but we do tumor imaging studies and PET has becoming increasingly important. We do a lot of studies for neuroblastoma too. Radiation exposure from diagnostic pediatric nuclear medicine procedures is acceptable. You can make your comparisons between different radiographic procedures and between nuclear medicine procedures, as has been alluded, using effective dose, and I am not going to explain the equation again since people have been through that.

Here are some examples. CT of the chest using low dose, recommended pediatric techniques, about 0.6 rem for chest, abdomen, pelvis is the standard rem for the cancer patient for screening. Gallium is going away. This is where technology is helping you, going to PET which has about the same amount of radiation dose as CT but has some advantages in terms of increased sensitivity and specificity. IOM-23 has proved invaluable in tumor imaging in children, about half what we are talking about with a low dose CT or with a PET scan.

I am going to skip through this because people have been talking about the radiation limits in the current regulations, except to get to this and repeat it, for a research patient under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in the adult regulation. This means single dose, whole body, active blood forming organs, lens of the eye, gonads of 0.3 rem annual and for other organs single dose 0.5 rem. That is not the say that radiopharmaceuticals work. There is an excretion pathway for most radiopharmaceuticals and this 0.5 rem is incredibly restrictive. It is not so much on the whole body dose end, which is itself an obsolete method of measuring things, but it is the target organ doses that are ridiculous. The target organ doses are now in the effective dose calculation so that risk is included.

This greatly limits the ability to study new PET agents in children with cancer or otherwise life-threatening or life-shortening diseases. We are not talking about children off the street out

of the fifth grade class in terms of doing this research. We are talking about children who have cancer, children who have for example congenital heart disease conditions that even though they are corrected, some of them may not have a lot of life expectancy beyond 30 or 40 years, and other congenital diseases which, although progress has been made, may have significantly shortened expectancies, life expectancies.

For example, we have made incredible progress with lymphomas, Hodgkin's disease, non-Hodgkin's lymphoma but, still, of the patients who come in with that diagnosis probably 10, 12, 14 percent will fail their initial chemotherapy or relapse at some point and succumb to the disease. Then an additional, perhaps 10 percent, will bet second malignancies. So, even in one of the great successes in pediatric therapy for cancer, it is not without risk. Neuroblastoma, the most common solid tumor in children under 10, the common type that you see over one year of age, only about a 40 percent survival rate with extremely intensive

therapy. There is an incredible need for research in this area.

Radiation doses for most PET radiopharmaceuticals far exceed the 0.3 rem whole body and the 0.5 rem to any organ. But this is where things are helping. As I pointed out, FDG has actually reduced radiation exposure because it is available at this point. These limits may also pose a problem for studies using new single radiopharmaceuticals as well. Here are some examples. Fluorodeoxyglucose, effective doses for an adult, for a 10-year old and for a 5-year old. Notice that it is somewhat lower for the standard dose on a microcurie per kilogram basis. But look at the bladder wall doses. But this is included in this risk figure so there is no need to have separate exclusion for this.

Here are some other agents which have been described in adults that have had some utility. I do not know whether these will be useful in children but we may never know unless we are able to explore these things. Fluorocholine,

fluorodopa, fluorothymidine, C-11 methionine. Even with the advantage of a short C-11 radiopharmaceutical we are looking in the bladder wall effective dose that is prohibitive under the current regulations but, again, this risk is included here, under effective dose.

Well, why not reduce the administered activity by 50 percent for your fluorine-labeled compounds? Well, even with a 50 percent reduction the target organ doses are going to be out of the range with the current regulations.

Effective dose, not whole body dose, as has been said over and over again. And, I might just point out that the target organ dose for most radiopharmaceuticals is usually much more than the 67 percent above the whole body dose or the effective dose but, again, the risk is in ED.

Radiation exposure limits--well, we have been talking about that. The pediatric dose limits that hold the investigator to 10 percent do not allow needed research in patients who have cancer, other diseases that are life-threatening or

significantly shortened life expectancy.

Recommendations--the effective dose concept should replace the concept of whole body dose. An upper limit for target organ dose should not be necessary. The effective dose calculation takes into account almost all of the risk associated with exposure to individual organs. The upper limit for effective dose should be higher for children with cancer and other chronic life-threatening diseases.

Parenthetically, I would like to point out that there should not be an exclusion in the new recommendations for this more than minimal risk category. More than minimal risk includes everything from children who may be a little bit more uncomfortable in taking a written psychologic exam to children who will be in cancer therapy protocols, who are at risk for death from the toxicity of the agents themselves. If you want to classify these things as more than minimal risk, which has been done, we are talking about trivially more than minimal risk and the RDRC regulations

themselves, by limiting radiation exposure and by limiting the amount of noon-radioactive components to very, very low pharmacological levels, define the risk and we do not need an additional definition.

An upper limit of effective dose of 2 rem for single dose and 5 rem for annual and total effective dose should be considered in these patients who have cancer and life-threatening or life-shortening diseases. This will facilitate needed research with positron-emitting radiopharmaceuticals.

Unless the RDRC regulations that are changed, the new molecular imaging technology will never be applied to children. The expense will be driven way up and will be extremely limited, and those potential benefits will not be available. An up to date standard should be developed based on effective dose. And, finally, the RDRC mechanism should clearly permit use of a wide variety of labeled molecules as long as the molecule is given in doses that are far below pharmacologic doses.

Thank you.

DR. MILLS: Dr. Gelfand, thank you. Dr. Kim Williams is our next speaker.

DR. WILLIAMS: Good morning, and thank you for allowing me to participate. I am Dr. Kim Williams. I am currently the President of the American Society of Nuclear Cardiology. I am also the Chair of the Radioactive Drug Research Committee at the University of Chicago and am a practicing nuclear cardiologist. So, I am actually wearing all three of those hats today.

The American Society of Nuclear Cardiology, for those of you who are not as familiar with, represents over 4500 physicians and medical professionals primarily doing nuclear cardiology. We are an organization that is educational, primarily developing training guidelines and practice standards and doing accreditation or promoting accreditation and certification.

Today I would really like to confine my comments to the pediatric imaging issue. It is a

problem that comes up not infrequently, perhaps not as much as in Dr. Gelfand's unit but we get requests and don't have current guidelines.

It is something that when you look at it in a comparative sense, we have children who, again as Dr. Gelfand said, are not coming off the playground. These are people who have significant illnesses that have to be dealt with and there is a wide variety of ways in nuclear medicine to deal with some of these issues, but there are also competing techniques which may not have the advantages that we have in nuclear cardiology.

So, the real questions are should the pediatric research be exempted from the IND process? We have discussed a lot already today that the IND is not required if the radiation does not exceed 10 percent of the adult dose, but the 10 percent really does present a problem for those of us who do clinical imaging. So, what we are hoping is that there will be a change in the number of barriers and lowering the regulatory barriers that the FDA currently has that are preventing a lot of

the research that could be done from occurring.

We have talked over and over again about the 10 percent rule and how it is unencumbered by actual data so I won't belabor the point here. But from the clinical imaging point of view, I would like to sort of reverberate off what Dr. Hall said. If you divide this into two groups--and he was proposing 0-5 years and 6-18 as the two groups--clinically those really are the two groups because under 5 years old you are going to get very little cooperation. We frequently have to do sedation which increases the risk, and we actually like to keep the doses relatively high so that the images can be quick.

On the other hand, with the older children who are able to actually cooperate, we can actually increase the acquisition time, double it, triple it perhaps if we have a very cooperative patient and image the heart at half or third of the dose. But the clear issue is that all of this is being done clinically without FDA guidelines because they don't exist right now.

So, we are hoping that the FDA will initiate pediatric research and that there will be cooperation between the subunits to try to review the issues as they come up. The written request letters that were discussed in the February meeting really should be issued to grant pediatric exclusivity and, hopefully, we can revise the 1/10.

The barriers to research have already been discussed and i would like to sort of focus on this one slide, on point number four, which is that we have to keep in mind that from a clinical point of view research and imaging with radioactive agents is often a very less risky proposal than, for example, invasive testing. In our lab, what we are called to do is particularly Kawasaki's disease, which has aneurisms of the coronary arteries, and the patients who have congenital coronary anomalies. The question is do they have significant ischemia of the muscle that is going to put them at risk. The option is between doing a noninvasive test that does not always give the proper information, such as an echocardiogram, or

doing an invasive test, such as cardiac catheterization that is then going to give us three problems. One is that vascular access is always difficult, fraught with more clotting and bleeding from the arteries and veins. The second one is that you are injecting a non-radioactive dye but a dye that has substantial problems, particularly if there are diabetic kidneys involved. Thirdly, if you look at the effect of dose, the cardiac catheterization actually can have significantly more radiation exposure than what we are avoiding doing.

So, this sort of comes into the area where perhaps the 21 CFR 50, Subpart D 50.54, talking about clinical investigations that are not otherwise approvable but present an opportunity to understand, prevent and alleviate serious health problems and welfare of children really should come into play here.

So, until more pediatric data is available, I can't see that it is easy to change the existing rules and we are hoping that the FDA

will continue to prioritize this issue and give us more guidance. Thank you very much.

DR. MILLS: Dr. Williams, thank you. This concludes our established speakers that we had this morning. I now have about 18 after the hour so we have approximately one hour of open public microphone for anyone who would like to come to the microphone and make comments. At this moment, just before we start that, I would like to thank our speakers from the public this morning, as well as from the FDA. So, anyone who would like to make public comments, please come to the microphone. Thanks you.

DR. HOUN: Also, the agency is hoping to get more clarification and understanding of what the research community is thinking in terms of advising changes in our regulations. Also, I am encouraging the FDA folks, if you have questions of the speakers that we ask as well so we can understand better people's positions. Thanks.

DR. MILLS: If you would identify yourself, please, sir?

DR. WONG: I am Dean wong. I am a nuclear medicine physician, Professor of Radiology and the Vice Chair for Research Administration and Training at Johns Hopkins.

I am primarily a PET and SPECT researcher in CNS work. I have had about 15 or 20 INDs since the first receptor IND done with dopamine in 1983 and a number of RDRC applications. One concern that I have is that until the radiation limits are changed, if they are changed on the RDRC, we are faced with the problem when we have ever increasing complex radiotracer studies where some of the tracer studies are under IND and some of the tracers are appropriately under RDRC. In each case separately they are appropriate and they are ruled by our radiation committee, RDRC and IRB and the FDA is being appropriate.

But when we do the two of them in the same individual, which is increasingly common, we find that we are hampered in that at least our committee is interpreting the regs as having the RDRC rules with organ dosing, which as we have all heard today

is perhaps somewhat archaic, trumping the IND rules which, at least at Johns Hopkins, is effective dose. This is often interfering with the ability to do multiple tracers in the same person even though each tracer is pharmacologically inert and has been well characterized by our institution and others. At least until the radiation limits and the organ dosing has been changed for RDRC, I would like to see some clarification on deferring RDRCs from requiring the organ dose being applied to IND tracers when they are both used in the same IRB application.

DR. HOUN: So, your institution does not say that then the study should just all be under IND?

DR. WONG: No, it is just the opposite. The current RDRC interprets the regs as requiring everything being under RDRC.

DR. MILLS: That is to reflect what they perceive as the limitation in terms of the radiation exposure?

DR. WONG: That is correct, just for the

radiation exposure issue not for anything else of course.

DR. HOUN: Right. I think that Dr. Panholzer was making the point that you can do an IND for a study that meets RDRC requirements or for a study that does not. It sounds like initially your study for the radiotracer alone may need the organ dose limits but that, as you make the study more complicated or with other drugs, it will exceed. That other drug, you are saying, is under IND. Cannot the whole multi-part component be under IND?

DR. WONG: It could be, but that would require taking an established tracer that has been used for RDRC for a number of years and then amending INDs. Let me make that a little more clear. It is quite common it is the reverse. Often at Johns Hopkins we start primarily with INDs for the brain tracers because we were asked to do that. It happens that there are a number of tracers where it makes sense to recant from that RDRC. So, when we combine them it is not a

historical issue; they both developed in parallel. It is just that sometimes scientifically it is important to study them both at the same time. And, the current rules makes the RDRC trump the IND and I think that that is inappropriate. The only alternative, as you just pointed out and Dr. Panholzer mentioned this morning to me at the break, would be to incorporate the RDRC into the IND. But then that requires an amendment. So, it is a bit cumbersome. I agree that that is a possibility but I am pointing out that this is an anomaly which comes out as studies become more and more complex. But this is going to happen in multiple centers. Hopkins is not going to be the exception here and you have to deal with it.

DR. MILLS: Other comments?

DR. GELOVANI: Yes, I am Juri Gelovani. I am currently at M.D. Andersen Cancer Center, recently moved from Sloan-Kettering, in New York. I would like to pose the question which in my opinion represents a conundrum in terms of new imaging agent development, whether in context of

new therapeutics or in context of new molecular imaging tracer development per se. That is related to the concept of pharmacologic dose as well as the first-in-man. The conundrum is as follows: In order to proceed with the evolution of a new tracer for the purposes of not diagnosis but for validation or evaluation of a physiologic, pharmacologic but most importantly molecular biological process, for example DNA proliferation, or certain signaling from receptors, or intracellular signaling proteins, enzymes, receptors are probably not the most appropriate example here but, say, PI-3 kinase, the imaging agent.

So, it is hard to even think that the new radiotracers have to undergo validation as new drugs with respect to the assessment of the pharmacological doses and their toxicity and potential side effects because basically first-in-man precludes generation of any data that could be used subsequently in radiolabeling the molecules and then injecting them for diagnostic or

RDRC qualifying studies, and the limit usually for these type of studies is toxicology. So, on average the toxicology for a new molecule in preclinical studies will cost somewhere from 50-100,000 dollars and if somebody is developing a radiotracer, not just by radiolabeling drug or by altering its pharmacokinetics, albeit yet under these pharmacologic doses in picomolar concentrations, you will have to go through four or five different molecules, and developing toxicity profiles, full-blown toxicity profiles as one would do for an IND, really is hampering the progress here. Then, you cannot develop a new radiotracer or a new drug if you don't have the toxicity data and in order to proceed for full-blown evaluation of toxicity and discard all those candidate molecules that are not even worthy to pursue there is no way to radiolabel and inject first in microdosing equivalent like in Europe and study those.

So, the question is how the new regulations or amendments could be introduced

either in the RDRC mechanism or simplified IND to reflect that critical need. My suggestion is could we introduce for some of the studies that would involve newly developed radiopharmaceuticals, candidate molecules, under the RDRC but including FDA-recommended safety monitoring criteria so we don't have to do full-blown toxicity studies until the lead candidate and the most promising candidate is identified in the pre-IND study type of situation to move into full-blown toxicity studies and the IND.

DR. MILLS: Dr. Collins, would you like to comment on that?

DR. COLLINS: Under the existing regulation we really have no choice, but if you were to propose something different than the existing regulation what would be the safety criteria that you would use for allowing a novel molecular structure to go into humans that would meet your criteria of encouraging innovation but maintaining human safety? You mentioned clinical monitoring. That is excellent. But before it goes

into people, what would be the minimum safety package that would make investigators comfortable and IRBs and RDRCs comfortable with first-in-human studies?

DR. GELOVANI: It is hard for me to represent the group here, and I don't want to be penalized afterwards if I suggest something that is not agreeable to everybody, but from the logical perspective it would be to validate our commonly accepted statement that picomolar or low, low micromolar concentrations of the cold equivalent of a radiolabeled tracer in animals is not causing at least noticeable weight changes, something that is, you know, more reasonable as a pre-IND toxicological study but not full-blown toxicology study involving, you know, histopathology and genotoxicity and so forth. This could be debated.

On another hand, some of the molecular structures that already are known and are deroutized from the drugs, for example a known pharmacophore that is being used in other applications for therapy, or there is a history of

using these pharmacophore but without the pharmacokinetic deroutizing groups on it or, you know, fluorine added to the molecule, at least demonstrating that there is no some kind of death of animals or pronounced changes in the phenotype after pharmacologic dose or imaging dose was administered to the animal to be at least accepted as preclinical data.

I think another comment here that has to be addressed towards, for example, the antibodies where we know that the majority of the humanized or even murine antibodies--we know what their toxicity profile is, or antibody fragments even for those which are approved. Now, when we know that the immunogenicity is an issue and the specificity of the antibody does not add to the immunogenicity, if anything, it adds for the targeting. So, the pharmacokinetics and biodistribution of antibody class or its fragments class is usually known by direct iodination and how it performs, and so forth.

So, if we are studying for example new

antibodies for the new ligands, new epotopes, how that changes the known pharmacokinetics and the profiles of the antibodies in terms of their changes of immunogenicity--I don't know how that applies because the only change in the antibody is specificity in the hyper-variable region. So, why all of a sudden we have to go through all the toxicity all over and all over again is beyond me.

If you are trying to do the Iressa and take the Iressa derivative and chop off morfolino group and put, for example imidazole group how does that change the toxicity? We know that that grouping doesn't even alter the binding to the target. Can we start introducing the structure specificity activity and enzymology data to prove that, that we don't have to go into the full-blown toxicity studies, at least in those institutions or those cases which can provide this information?

DR. HOUN: My other question to you would be are you saying that that would be also safe for adults and pediatrics, or that pediatrics would be a different concern?

DR. GELOVANI: Depending on the group. I am voicing an opinion from the cancer field and I think that if you start comparing the risks versus the benefits, especially for the pediatric population where the data is, if I may generalize, almost non-existent in the new radiotracer category, then I think that should be applicable because for some kids there is no hope at present.

I will give you a specific example. What dosimetry are we talking about if a child is already irradiated and the bone marrow is ablated? And a transplant is given, and what we want to do is to establish a technology which identifies the early foci of leukemic disease before the full-blown manifestation of disease will be detectable by blood counts. Using imaging, we can detect these early foci of disease--if a child got more than--I don't know--10, 20 Gray, the whole body.

PARTICIPANT: My name is Bob. I am from NIH, doing research in PET, and I wanted to address the question of pharmacological dose that I think

Dr. Collins raised. I was in the back and I couldn't see. But how would you know on going into initial human studies with a new chemical entity that you would expect to be a tracer, trace pharmacological doses?

The argument I am going to make is basically that you could do that with good scientific justification, in my opinion, based up receptor occupancy. If you know the radiotracer is occupying a small percent of the target sites relative to the percent needed for pharmacological effects, then you would have a good safety margin and one of the best ways of assessing whether there would be pharmacological effects. That is the bottom line recommendation.

This sort of goes back to my training as a pharmacologist in measuring a dose-response curve. You have a dose given and some sort of biological effect and you want to know what the lowest does is that you can give and not have an effect. Well, you can measure the dose in various ways. You can do it orally and then scale up. But orally isn't

that good because you don't know how much of it makes it into the bloodstream. So, instead, you could try to have a dose-response curve for the plasma curve. But even there you don't know whether the drug is going to get from the plasma to the receptor.

So, what I was generally taught and I think would be valid, the best dose-response curve that you could get, which would overcome all of these issues of biodistribution and access to the target, would be receptor occupancy versus response. So, I think there could be a scientific rationale that actual target receptor occupancy is the better measure of "dose" than these others that could be influenced by absorption and distribution.

So, I think many of the people in the field, including myself, "know" that we are giving tracer pharmacological doses that shouldn't have any effect. I think one way to try to show that would be, for example, with regard to receptor occupancy. An example would be with regard to D-2 receptor imaging in the brain. The first

pharmacological effects that probably occur are akathisia. Based upon studies done here and in Sweden--in the United States and Sweden, it seems that akathisia, restlessness, begins at about 50 percent receptor occupancy. If you can show that the tracer that you are giving is going to be occupying less than one percent, then you have a 50-fold safety factor and you have overcome any issue about whether the drug makes it into the brain or not because you are looking at the specific target site.

So, all of this is based upon the idea of receptor pharmacology and I guess an overall question would be, well, should we only be looking at receptor effects? Here I believe it is true--but I would appreciate input from other knowledgeable pharmacologists and FDA people here--that if you give really, really low doses the only effects or side effects you should be looking for are receptor mediated and not non-receptor mediated. If you give really high doses it is clear that you can have effects not only at the

target receptor but also on the liver and have toxicity. But if you have very, very low doses, then what it means is that in order for the drug to be active there has to be some target site with very high affinity. By definition, a target site with high affinity is a receptor by the way in which it is typically termed.

So, the rationale, in summary, is by giving low doses we know that any effects and side effects would be mediated by receptor. You can feel comfortable that there would be no pharmacological effects if you know the pharmacological effects begin at a certain receptor occupancy and the tracer would occupy a smaller number. With this sort of information, which can be gathered from animals, it would avoid the necessity of an expensive--someone said 50,000 or 100,000; my recent pricing is 250,000 dollar animal tox. package for each new compound that would try to go ahead. Thanks.

DR. SWANSON: Dennis Swanson, Director of Research Conduct Compliance Office, University of

Pittsburgh, also Chair of our RDRC. In answer to your question about if we allow first-in-human studies based upon animal toxicity data, what is an appropriate level, I would actually pose that question back to the FDA. Today you get IND applications for non-radioactive drugs where they have animal toxicity data and, therefore, proposing first-in-human Phase I study. What does the FDA feel comfortable with in allowing such a study to go forward or being accepted?

So, I think you probably have more experience in that regard than we do. So, what are your stable pharmaceutical people saying with regard to what they consider to be an appropriate factor? I also recommend that you might want to look to what other countries are doing. I think it is interesting for example, if you look at Sweden--we actually had a situation where a compound was developed at the University of Pittsburgh, was taken to Sweden to do initial human studies because their regulations do permit first-in-humans under a very limited set of animal

toxicity studies. In fact, a group in Sweden has published a very interesting paper, entitled, "Positron Emission Tomography Microdosing, a New Concept with Application in Tracer and Early Clinical Drug Development." They reference an EMEA committee guideline position paper on non-clinical safety studies to support clinical trials with a single microdose.

They also reference an ICH M-3 recommendation for safety pharmacology single dose toxicity studies and repeated toxicity studies which basically propose an extended single dose toxicity study, which includes a control group and sufficient number of treatment groups to allow estimation of the dose inducing a minimal toxic effect. For compounds with low toxicity a limit dose could be used. Allometric scaling from animal to man, using a safety factor of 1000 should be used to set the limit dose. Both genders should be considered. The study period should be 14 days and include interim sacrifice at day 2. The study should be designed to obtain information on

hematology, clinical chemistry and a minimum of 2 time points, day 2 and day 14, and histopathology--in ICH M-3.

DR. MILLS: Dr. Collins?

DR. COLLINS: As I mentioned in my talk, we are considering the use of exploratory INDs, which has a lot of overlap with the EMEA guidelines. In each case, as you describe, the advantage, although there is a simplified toxicology package, is that our staff or the EMEA staff be able to look at each one on a case-by-case basis. So, you know, it is a tradeoff between the general flexibility allowed under the RDRC, with the caveat that it can only be where you already have human experience, versus going forward under a simplified IND where we can look at each package and not require multi-dosing, multi-species, all of the requirements for standard therapeutics.

So, our agency has committed to publishing a guidance document on exploratory INDs within the next two months, and with a lot of documents in the pipeline it is hard to meet those deadlines

sometimes. But we are quite cognizant of the EMEA guidelines and it is not a competition between Europe and the United States, but we think there is merit and studies can be done safely if there is some level of oversight by our staff. So, that is fine for us. If we are hearing from people that the IND process is a huge barrier, then we need a dialogue on how to make that barrier lower while maintaining safety. And, one of the advantages of having a case-by-case basis is that we can look at the individual cases and do that.

The RDRC process--we are locked in. It is the regulation that says there has to be human data. It would require change in the regulation. If somebody wants to propose that, that is why we are having a public hearing. But for the IND process we have the ability to be much more flexible in providing a guidance. All the IND regulations require is that we be assured that it would be safe to proceed. So, we will try to meet our timeline to get the exploratory IND process out because we have heard that in more than one forum.

DR. MOSLEY: Hi. David Mosley. I am a nuclear medicine physician. My current employer is Eli Lily and Company, in Indianapolis. I am their medical advisor for imaging technologies.

We would like to endorse the concept of this simplified or mini-IND. We are confident that that is what we need to pursue our goals for using radiopharmaceuticals in research. As you revise your regulations for the RDRC and for radiopharmaceutical specific INDs, we would like to encourage you to become more explicit with respect to your definitions on specifications, policies and procedures.

We have a lot of trouble working with RDRCs for a variety of reasons. Standards don't seem uniform to us. As a consequence, the risks that we engender using different RDRCs become prohibitive. For example, at the break we talked about the need for a new definition for a clinical trial in this context. I cannot understand how anyone uses the RDRC to conduct a receptor occupancy study, for example, because that seems to

meet my company's and my former university's definition of a clinical trial, and 361.1 says quite explicitly in three places that this mechanism may not be used for a clinical trial.

So, given that the RDRC in its current concept is closed off to us, what we need is a process for using a centralized mechanism that is a federal mechanism, one where there are standard definitions, standard assessments of risk, but doesn't require the task of publishing an IND that is required for a conventional therapeutic drug. That is, we prefer to submit INDs to the central governmental authorities but we need some relief because when we use the same processes that we do for conventional therapeutics the timelines get very, very long and the cost becomes so prohibitive that, in essence, the costs are higher than just doing conventional clinical trials without these radiopharmaceuticals and, therefore, we are frequently stuck.

So, again, my message is to help us with the central process, the mini or simplified IND, by

becoming much more explicit with your definitions. Thank you.

DR. MILLS: Dr. Collins, do you want to respond to that?

DR. COLLINS: We are happy to have that endorsement. Now, we have run into an issue where very large organizations don't really like small--two tracks. They will do everything to the same very high standard. We can't change that; we can only offer it as an alternative. As an example, I would mention the regulations the FDA has on Good Laboratory Practices, 21 CFR, Part 56. There is only a narrow spectrum of preclinical studies that are required to be conducted under those regulations but some organizations have told us that, well, it is easier just to do them all under the same one. So, you know, we can offer the alternative but people have to step up and use it.

DR. MILLS: Please?

DR. AKINSAMI: Thank you. My name is Lawrence Akinsami. I am a physician and at the same time I am a pharmacologist. I am the global

lead on early development for my employer, the H.D. Medical Research up in New Jersey.

Recently, the EMEA has been talking about micro-dosing for micro-dosing technology that is available that you just talked about. Of course, they come up with micro-dosing CT just like the IND. Recently too, the FDA Commissioner talked about exploratory IND and, again, the NCI, in conjunction with the Division of Oncology, are proposing facilitated IND. You know, these are ways to shorten and reduce the obstacles that we all perceive that IND poses to, you know, drug development, especially in these cases.

Now, this particular division--I want to know, please, if you don't mind, what would be your contribution or support? Are you going to support the facilitated or the exploratory, or do you want to combine? What would be your own, you know, contribution to make sure that the obstacles that are posed are greatly reduced? Thank you very much.

DR. MILLS: Jerry, do you want to start?

A couple of things, number one is that the conversation and the discussion so far has raised a spectrum of entities, if you will. Micro-dosing, which we understand and have had discussions about, and I think we will have a speaker this afternoon who will be discussing that. Colin Garner will be talking about micro-dosing from that aspect. We also are looking at the exploratory IND, which is a developmental process which we are in the midst of right now, working on a guidance coming forward, and that has very high support and looking at that interface with RDRC.

Right now, I think that part of this discussion would be best served for everyone in the audience in the next few minutes, if you would like to come and discuss where you see the interface between RDRC and where you see the interface between this type of exploratory IND, a low tolerance, low barrier type of IND experience, to be looking and going forward with.

Certainly, I hear industry at this microphone just now pointing out to us that the

RDRC mechanism is difficult for them to approach and utilize effectively in drug development. Certainly, there are a number of people in this room that effectively use RDRC for early development studies. So, there are actually two groups within this room, and they have talked to me many times about these issues. Here is your moment, in terms of that interface, to give us that input as to how you see the two and where you see the margins between these two in an effective way so that we can go forward in looking at exploratory IND and looking at RDRC development.

I anticipate that going forward, both of these entities will be growing and we will be getting input so this is your opportunity to look at the two. Certainly, we are fully supporting of the idea of an exploratory IND development through guidance and looking at how we can lower those barriers for industry to be able to look at drug development in an effective way. At the same time, we are looking at RDRC development and looking at a 29-year old regulation which, frankly, has looked

quite well over the years but probably needs a little trimming and adjusting right now from the input that we have heard this morning. So, I would invite people to come back up to the microphone. Dr. Collins, would you like to make some comments?

DR. COLLINS: Well said!

DR. ZIMETKIN: My name is Alan Zimetkin. I am a child psychiatrist with the intramural program of the National Institute of Mental Health. I am the Deputy Director of the NIH Radiation Safety Committee, and I am also a member of the National Institute of Child Health and Development IRB.

In the late '80s and early '90s I was a principal investigator on between five and ten PET studies involving minors, and we published several of these studies in The New England Journal of Medicine. It was not without the help of radiation health physicists such as Lisa Cordenado who made pour ability to stay within the regulations and that, as any of you may know who are interested in pediatric PET, involved normal controls.

Now, my only two points that I would like to make are that, having recently heard what I consider a brilliant lecture by Ludwig Feinendegen--I can't really pronounce his name but many of you probably know his work. He is the Chairman of the International Committee on Radiological Measurements. I am unconvinced that exceedingly low levels of ionizing radiation carry risks. I think this is a very debatable point.

What I am convinced of, however, is that the entire field of child psychiatry and child neurology has moved away from PET in favor of functional magnetic resonance imaging and I see this as a huge problem. FMRI, as we all know, is risk-free from radiation. You can repeat scans many times. You can do it over time. I mean, it is the easy way out, in my opinion, for studying brain chemistry in developing organisms.

As further evidence for my passion really for studying kids under the age of 18, there are two diseases that I would like to highlight--how critical this infrastructure needs to be to

understand pathophysiology. One, of course, is the Lesch-Nyhan disease. As many of you know, many of these children don't survive past age 19, 20, 21 or 22. They have no motor control; they are in wheelchairs and despite early reports they were mentally retarded, it is pretty clear that they are not. They don't survive. It is a wasting disease characterized by chewing fingers off; chewing lips off and self-mutilation. We showed very low levels of dopamine in the brains or almost no dopamine in the brains of these kids.

Another problem that I think everybody is aware of is the national epidemic of obesity, and this is something that I have become quite interested in, and applying PET technology to understand this. As you know, we can study people who have had obesity for 10, 12 years after the age of 18 but I think it is going to be increasingly more important to study kids at risk for obesity and kids who have not suffered the sequelae of low activity and medical complications. It is clear that this is a disorder that shortens life.

So, why am I up here? My plea is really to facilitate the use of radiopharmaceuticals in pediatric age populations. We have been able to do it but we are not doing it any longer, and only in an exceedingly limited way, and we are very skilled, having such expertise in the intramural program, such as people like Peter Herskovitz, to modify the procedure to get within the dose limits. But given the paucity of data on the risk, I think it is imperative that this committee reconsider those dose limits.

One last thought is, wearing my IRB hat for a minute, I really have a lot of trouble with our definitions of minimal risk and above minimal risk. This is a little bit like the duck test, you know, if it quacks like a duck and walks like a duck. I happen to have two teenage adolescents driving, teenage daughters, and I have to tell you being the parent of teenage daughters is a highly risky business--

[Laughter]

--as many of you probably know. You know,

when I go over to that high school and see varsity football--and my daughter played ice hockey, of all things--I mean, I do really think that worrying about these levels we are sort of out of touch with the real world. Now, I understand I am in the intramural program and we may be in an ivory tower, so protected from the real world of litigation and advocacy groups against doing research that when I consider the number of PET studies I did in 12-18 year-old kids and their siblings--I mean, that is how we got permission to do them because we argued that siblings of autistic children or siblings of Lesch-Nyhan children are affected by the condition.

Now, one can argue the ethics and morality of that. This is water that is well over the dam. But my other question is would a kid with two obese parents who has an 85 percent chance of being obese, who is not obese, have a condition?

Once again, these are not really under the purview of RDRC versus IND, but I think my purpose for mentioning this is just to raise a flag that those of us who are truly interested in studying

kids before the disease is so ravaging to live, such as in schizophrenics, that we need to convince our colleagues that PET in kids under 18 not only is possible but really a very good research strategy. Thank you.

DR. HOUN: Can we ask you some questions?

DR. MILLS: Exactly. Please don't leave the microphone; you are not getting away now! First of all, my daughter went through the teenage years and she is 33 now. You will make it!

DR. HOUN: But you will lose your hair!

DR. ZIMETKIN: I had a full head of hair--

DR. MILLS: So did I. We are here together!

[Laughter]

DR. HOUN: Tell us more. Was this all under RDRC?

DR. ZIMETKIN: No, it was all under IND.

DR. HOUN: And are you saying to facilitate more pediatric research under RDRC and that the dose limits are too low? I mean, be more concrete. Why is your institute not doing RDRC?

DR. ZIMETKIN: We are really not doing it because people have been scared away from doing PET, not because of the dose limits. It is the interest of the investigators and their perception that we can't get controls and that we can't do the research, can't get it approved. And, that is because it is so technically difficult.

Now, in a place like the intramural program we have the expertise if there was interest on the part of the investigators to do it. We did it under the IND and again, Lisa can correct me, because the dose limits were so much less restrictive versus RDRC.

DR. MILLS: So, you are not dealing with a regulatory barrier per se, you are dealing with the perception within your medical community in terms of the challenge and the technical difficulty.

DR. ZIMETKIN: Exactly, and also the IRBs. To be very honest, when we first went to do this we had Roger Borssy come up and do a presentation in front of our IRB, such that, you know, we really could look at issues. I also researched the

incidence of what minimal risk is. You know, 1/10 adolescents is in a car accident involving an injury, etc. So, we tried to really inform our IRB about what is part of the daily life. Again, my studies confine themselves to 12-18 year-olds which, arguably, is a different set of life experiences than a 5-11 year-old.

DR. MILLS: Dr. Goldkind, would you like to comment in terms of the risks in terms of the challenge for the IRB and looking at those issues?

DR. GOLDKIND: Well, I agree with you. The concept of minimal risk and greater than minimal risk is extremely slippery and it is very hard to define carefully. I know that the Secretary's advisory committee is actively working on a guidance for IRBs in this regard and we, at the FDA, are also working on a guidance regarding those issues in conjunction with OHRP.

They have actually addressed some of the points that you brought up in terms of if it is socially acceptable to play ice hockey or football, does that mean that that is considered a minimal

risk category. Certainly, some of the things that we think are socially acceptable for our children to do are not what we would consider to be acceptable within the confines of research, particularly research that is not therapeutically beneficial. But we fully understand that there are issues with those definitions and we are trying to work forward with those.

PARTICIPANT: I wanted to comment on the crossover between abbreviated or mini-IND and the RDRC. One of the things that doesn't make a lot of sense to me under the 361.1 regulations is the restriction that we are allowed to do basic research studies but we are not allowed to evaluate it as a potential diagnostic agent. If you look at it from a research subject safety perspective, what is the difference? Okay? If we are still at whatever toxicity limits or if we are still going to be required to do it based upon prior human demonstration of no pharmacological effect, what is the risk difference? Why are we drawing this arbitrary line that I can't do an initial

evaluation for safety and effectiveness under the RDRC regulations?

So, you know, I would suggest that--I mean, in answer to some of your questions, I mean, the reason why people don't for INDs in many cases is because the IND requirements are really too excessive when it relates to what we are doing with radioactive drugs, and you have heard this in many areas. If we do a standard toxicological battery that would be required for a traditional drug, that doesn't take into account that radioactive drugs, especially those we are using in research, may be administered one time max, or maybe two or three times max over a yearly period. They are not administered on a chronic basis. So, the toxicity requirements that go along with an IND for a radioactive active used for research have to match what we are actually doing. The same thing, you know, what CGMP requirements are you going to impose on the radioactive drugs that are used for research when we now submit this for an IND? You know, we still haven't resolved that issue yet.

So, the answer to your question is going to be, you know, what are you talking about for IND and what are going to be the requirements associated with it? And, until we have a better understanding of that, then, you know, it is hard for us to address where the overlap might effectively be drawn.

DR. MILLS: Jerry?

DR. COLLINS: We are going to talk about quality afterwards but just be clear that, as with toxicology, the intent of our initiative is to have a sliding scale, that the quality standards that are in place for a drug that is being marketed or a drug that is in a very large Phase III trial are not the same quality standards that we expect for exposure to very small populations.

DR. HOUN: Also, in trying to answer the question about the difference for a diagnostic versus basic research, what was laid out in the regulations was that if the drug was intended for immediate diagnostic, like for patient decision, it is obvious that you want the level of quality,

reproducibility, performance standard for that test to be assessed because you are going to make a patient management decision or tell the patient a diagnosis. For immediate diagnostic use, that is not for RDRC. However, the crossover between trying to do research on a compound and would it have usefulness in a diagnostic situation, and the point when you think your principles or concept of research is done, yes, there is value and you want to advance and you want to make it a reproducible diagnostic test. That is when you want to advance to IND.

So, the early concept--it is difficult because we recognize there are certain overlaps where you may just want to start off at RDRC and then it would advance to IND, or you may not at all, depending on results or what you are looking for.

PARTICIPANT: Would it not though be reasonable to allow us to do Phase I and Phase II studies under an RDRC mechanism? Then, at the point where we have demonstrated safety and

preliminary efficacy, which is how you define a Phase II study, at that point when we want to proceed to Phase III studies, multicenter studies, that would be the point when we would submit an IND application.

DR. HOUN: I think at this point the way the regulations are constituted is that proof of concept is happening under RDRC. You saw the numbers, usually less than 30. It is obviously written for proof of concept.

PARTICIPANT: Now you have lost me. What are you trying to tell us? Are you willing to change the RDRC regulations? I mean, are we willing to change the RDRC regulations? Are you telling us that we have to keep the RDRC regulations as they currently exist and now we are going to try to fit things into that paradigm? What is the FDA looking at here? Okay?

DR. HOUN: The purpose of this meeting was actually twofold. One is to gather suggestions for improving the regulation that is 29 years old. The other obvious is that the regulation is not going

to change tomorrow, and it is about educating on what is legal now. So, we went through trying to give you an idea of what is required now, and right now you cannot do first-in-humans, and we are entertaining discussion, like, if we wanted to do this what would be some changes needed? What would be the safety requirements? So, that is twofold.

To answer the question now, less than 30 is what the regs say. It is probably constituted as a proof of concept type of endeavor as opposed to IND.

PARTICIPANT: A correction there. There is nothing in the regulations that says that less than 30 subjects is proof of concept of anything. The regulations simply state that if I do more than 30 subjects I have to do a report to the FDA. You know, to me, the concept of what is an appropriate number of patients to do in this research study is based upon scientific statistical justification of the number of subjects, not a limitation of 30 subjects. Okay? And, the regulations don't anywhere say 30 subject is a proof of concept.

DR. HOUN: No, I am just telling you that many RDRCs have allowed hundreds of people to go by. That is probably a time that folks have to reassess on whether they are really doing basic research at that time or another purpose.

PARTICIPANT: No, you base that on statistical justification of the number of subjects. As part of the RDRC requirements, you are also required to evaluate the scientific merit of the protocol. If that protocol does not have a statistical justification for the number of subjects then you, as the RDRC, are not doing your job in evaluating both the science of the protocol and limiting the number of subjects that are exposed to the radiation.

DR. GELOVANI: Gelovani here again. In the spirit of discussion, coming back as George Mills invited us to participate and further expand on this issue, and just having heard what was just said about the suggestions, can I make a motion, if the chairman here would allow us to make some sort of either vote or raising of hands type of thing,

whether we concur with this type of approach or not?

The motion would be to append the current reg and allow first-in-man with contingencies, not necessarily for all of the drugs that could be regulated as they are regulated now and have already been shown--

DR. HOUN: This is not a voting meeting, but everybody should write public comments to us because you have come here with your views and experience and we need to understand them. Our dockets is open. There are more people sitting here than there are letters to us, telling us in writing, with their thoughtful comments, how to amend. I really think that probably many people here represent different ideas and different interests and we need to hear all of them.

So, the public microphone is open because your comments will be recorded in a transcript so we can review them. But also really important is that you can spend much more time writing to us, and all your letters are going to be reviewed

because we want to carefully assess all parts of this regulation. So, you are welcome to voice your views and others can come up, but I think you are going to have the most impact if you provide us with written specifics and even change it to X way; change it to Y way. It is just much more concrete and we can evaluate that better than general sentiment of we need to be looser. What does that mean? What are the safety requirements? You need to help us figure that out.

DR. GELOVANI: Definitely. Now, the safety requirements which are for these simplified INDs are being developed somehow, I understand. If, at least to a certain degree, a block of regulation could be added to the existing RDRC but not applied to all the RDRC regulated imaging agents that have already been, for example, shown to be effective or safe in man, but to introduce this developmental part into the RDRC where one would use similar safety precautions, toxicological evaluations and provide also the conduit to direct interaction with the FDA through the RDRC

mechanism, because RDRC is part of the FDA, and utilize similar IND--minimized IND or simplified IND provisions within the RDRC mechanism for regulating first-in-man. Thank you.

DR. MILLS: I think that has been the recurring theme at the microphone in terms of the toxicology and the areas that we are looking at under RDRC and looking under IND and expedited INDs. So, those types of comments will be very valuable to us in terms of looking at the margins between these interfaces between the IND and the RDRC. It is an area that is obviously focused and sensitive.

DR. CORDENADO: My name is Lisa Cordenado. I am a health physicist and a subject matter expert in radiopharmaceutical internal dosimetry at NIH. I also serve as the chair of the RDRC. I got my first introduction to RDRC in dosimetry with Ray Farkis, back in the mid '80s when we were looking at radiochemical impurities.

I have a question because I am puzzled by something here. Dr. Goldkind, in one of your

slides, slide number 10, when you talk about Subpart D and you make this bullet, radiation exposure prohibit classification under 50.51. 50.51 is not involving greater than minimal risk. What is the basis for that statement?

DR. GOLDKIND: It was the sentiments of this group that radiation exposure would be more than minimal risk for pediatrics based on the information that we have.

DR. CORDENADO: So, it is a sentiment but it is not a mandate, an edict or regulatory statute?

DR. GOLDKIND: Correct. My discussion was meant to raise a proposal for studying pediatric research under IND, and these are the discussion points that I laid out for that proposal.

DR. CORDENADO: I know this statement has posed problems for the 14 IRBs intramurally at the NIH. For instance, the one with the child health and development. One of the studies wants to use DEXA scans and bone age x-rays of the wrist, and the dose is very slight. They say that there is a

regulation that means that that radiation exposure cannot be deemed minimal risk and, therefore, is not approvable under Subpart D of 21 CFR 50. And, I don't think there is enough support for this opinion here for the IRBs to be putting that much weight on it and disapproving some studies that have very good merit.

DR. GOLDKIND: Well, you know, pediatrics is a very heterogeneous population and when we talk about kids who are adolescents, who are adult size, it is a very different situation than when we are talking about other age groups, as we have discussed this morning. That is one issue.

The second issue is that there is still changing data, as was described, about the radiation risks to various age groups within adolescents even under 18. So, that was what was behind this statement.

DR. CORDENADO: Okay. I appreciate that clarification.

DR. MILLS: It is about 13 after. Next?

DR. CALLAHAN: I will make it short. My

name is Rod Callahan. I am a nuclear pharmacist at Massachusetts General Hospital. I chair our RDRC, the radiation safety committee, and I am a member of the IRB.

One of the stated goals today was to discuss things that are legal today. On Dr. Collins' slide number 7 the question was asked can you add a radioisotope to a molecule that does not have the same atom in its structure and do that under RDRC?

As a chairman of the RDRC, I would be very reluctant to approve such a protocol because, to me, that is a first-in-human experience with a new molecular entity and I was quite surprised to see that the agency has allowed such studies to proceed. So, by putting this foreign atom into a molecule, have we not in fact made a new molecular entity that we are studying in humans?

DR. COLLINS: That is a point of view that probably half the RDRCs that are active take and the other half of the RDRCs take the other one. The comment from the agency was based on the

preamble to the regulation as was first proposed in 1974 and subsequently finalized in '75. The description of studies that were envisioned, thinking back 30 or 29 years ago, were studies in things where indium and technetium being added to molecules, and that there was no way to actually study--I mean, those kinds of studies would be permitted under RDRC even though there would be no way to do the human pharmacology on them, whereas the human pharmacology was done on the unlabeled part.

So, at the time the regulation was proposed nobody was doing 18-chlorine studies. That just wasn't happening or was just on its infancy, shall we say? But in the nuclear medicine community there were a lot of these isotopes that are not part of any therapeutic or any molecule that had human pharmacology experience. They were linked. They were isotopes that were linked in some way. And, the issue with the linker is also an important consideration. You need to have some kind of safety information for what is going on

there.

So, that was the genesis of how our working group arrived at the conclusion that this practice, which has divided RDRCs across the United States pretty much in half--that was how our interpretation went at that time.

DR. CALLAHAN: So, if you put a technetium atom into a new molecule, then theoretically can be studied under an RDRC?

DR. COLLINS: No, if you don't know anything about the molecule you are attaching the technetium to--

DR. CALLAHAN: Okay, a molecule that we know and we put technetium on it could be first-in-humans?

DR. COLLINS: Again, half the RDRCs are comfortable with it and half aren't.

DR. MILLS: Let me invite you to send to the docket those comments because, indeed, as Jerry is noting here, that is divided very evenly across the RDRCs as to whether or not such a linker in combination with a label onto a material is not a

new molecular entity. Certainly, I share the comments that you just made and the concerns that you just had in terms of getting definitions that are appropriate, especially when you realize in this audience where you could poll this audience and you could find as much as 50 percent of the audience going in each direction.

This is going to be our last comment. We are right in the time frame.

DR. SHUGANI: Hello. My name is Diane Shugani. I am at the Children's Hospital of Michigan. I would like to follow-up on this idea of what is minimal risk to children. The disorders of children are very serious even very early in life, even in the neonatal period, and the minimal risk in a baby who is receiving maybe daily chest x-rays or abdominal x-rays and who is undergoing CT scans for intraventricular hemorrhage the risk to that child on a daily basis is a very extreme one. And, I think that we shouldn't be eliminating the use of these powerful tools that can really impact on the lives of these children. These kids, again,

are being exposed to doses of radioactivity. They are being treated with drugs that have never been tested in children, and here we have sort of another example of how we are trying to protect children but then not doing studies in them, and I just feel this is a very serious issue.

DR. MILLS: Dr. Goldkind?

DR. GOLDKIND: I have three comments. First of all, the kinds of exposure that we think is acceptable, the kind of risk exposure that we think is acceptable as part of treatment is very different than what we think is acceptable as part of research, research in particular that is not directly beneficial. So, that is one issue that we need to keep in mind and tease out.

The second issue is that we are working in terms of understanding minimal risk better and making it a uniform or absolute standard. If we look at the exposures that these very sick children have and we use that in a relative way, then the end results of that are that babies who are sicker, children who are sicker are allowed to be exposed

to higher risk as part of research which is unacceptable. So, that is point number two.

DR. SHUGANI: I am sorry, I misunderstood. What is unacceptable?

DR. GOLDKIND: What I am saying is you have to look at the risks in an absolute manner in the sense that a chest x-ray, if it is completely unbeneficial, is a chest x-ray. It has the same risk for a very low birth weight baby who is being exposed to multiple chest x-rays as it might for another child who is not, with the caveat that the special population might have higher risk. It might be a higher risk procedure for a special population.

What I am trying to say is just because these babies are being exposed to multiple x-rays and procedures as part of their treatment is very different than allowing them to be exposed to it; it still carries--just because they are being exposed to that high level of risk does not mean that a chest x-ray necessarily changes in terms of its risk exposure to that child.

DR. SHUGANI: How are we supposed to advance the treatment for these children if we can't do research?

DR. GOLDKIND: And the third point that I wanted to make is that we are not at all proposing that this research should not go forward. We are proposing that the research should go forward under additional protections afforded by an IND.

DR. SHUGANI: Just to follow-up, our IRB and many IRBs sort of see the guidelines that have been set forth in the RDRC as the guidelines by which they will approve a study. So, when you have the IND with no limit, that doesn't give them any framework for saying whether they should give approval. So, they feel very uncomfortable going beyond the guidelines that have been set forth in RDRC. So, this has more implications to IRBs in guiding their decisions than just the RDRC mechanism. Thank you.

DR. MILLS: Thank you. Certainly, that is an area that we need comment coming in and input throughout the time till January 16th. So, we

really invite those comments. We are at the end of our time. In fact, we are five minutes over. It has been an excellent morning; excellent comments.

A couple of housekeeping things. Remember? There is a list of places where you can go to eat if you would like. If you are going to leave you have to check your badges out and you have to check back in. We are going to start at 1:30 this afternoon so remember that line this morning. This morning, obviously, we had an excellent morning with great comments and we will start again this afternoon with the same format. We will have three FDA speakers. Then we will break and organize the speakers and then come back and we will have the formal presentations and then we will go to an open microphone. Our first speaker this afternoon is Dr. Eldon Leutzinger. He will be addressing product quality issues.

[Whereupon, at 11:20 a.m., the proceedings were recessed for lunch, to reconvene at 1:30 p.m.]

A F T E R O O N P R O C E E D I N G S

Quality and Purity Standards in the Production of Radioactive Drugs Under RDRC

DR. LEUTZINGER: Good afternoon. I am Eldon Leutzinger and I am the Chemistry Team Leader for the Division of Medical Imaging and Radiopharmaceutical Drug Products. I am here to introduce the subject of quality and purity standards in the production of radioactive drugs under RDRC.

In accordance to current regulations, in 361.1, Subpart D(6), the radioactive drug used in a research study shall meet appropriate chemical, pharmacological, radiochemical and radionuclidic standards of identity, strength, quality and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted.

The Radioactive Drug Research Committee shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form.

Now, in consideration of what standards of quality and purity shall apply to radioactive drugs under 361.1 to ensure the safety of research subjects, we have recently become aware of two occurrences involving RDRCs. In one case, a material of non-pharmaceutical grade and labeled "biohazard," obtained from a chemical company, was administered without assurance that the product was cleared of viral contamination.

The use of materials so labeled and/or labeled "not for human use" might still be acceptable if the RDRC had exercised its responsibilities under Section (d)(6) and (f) of 361.1. However, the RDRC failed to properly address these issues in this case and failed to require the principal investigators protocol to include adequate tests to be performed to assure that there was no viral contamination of the end product based on the source of the material.

There were other problems involving production of the radioactive drug and formulation that attest to the lack of controls and potentially

compromise sterility and, thereby, created potential safety risks. For example, equipment used to carry out the radiolabeling reaction included reaction vials and transfer vials that were not assured to be sterile. A laminar flow hood was not used to prepare the product, and the product was not properly labeled and there were no quality control performance checks made on radioactivity measuring instrumentation.

In another case, an RDRC voluntarily suspended all research with the PET drugs produced in their facilities on the basis that there was absence of proper production and laboratory controls to ensure the safety of human subjects. Some of the problems identified included, for example, productions that involved divergence from established procedures, resulting in batch-to-batch variations, and lack of initial qualification of intermediate precursors and assessment of integrity following storage before their use.

Because of one such divergence from production procedures, and before the procedures

had been verified to produce the correct radioactive drug, a PET product of unknown identity was allowed to be administered to human subjects in an IND study. Now, the drug was also administered prior to performance of adequate quality controls, for example, tests for identity and residual solvents.

Additionally, analytical equipment in the laboratory was not routinely maintained and calibrated to ensure proper performance. The HPLC instrument for determination of identity and purity that was used was not an adequate system suitability test prior to the testing of the sample itself. So, it could not be assured that retention times and the p-carriers obtained were reliable. Sterility testing was not conducted properly, attesting to the fact that controls were not adequate to produce PET products with the assurance that they could be used safely for either IND or RDRC studies.

So, this is very concerning to us, and it is because of these kinds of experiences that we

are asking the following questions: How should RDRC ensure protocols meet chemical integrity and purity of precursors for use in radiolabeling procedures?

Changes made to established procedures suitable before being implemented in production of the product to be administered to humans? A radioactive drug molecule has correct identity? For example, how should RDRC ensure that protocols for identification are technically sound and have established mechanisms ensuring that the results of the production and testing are documented in sufficient detail for traceability from production to testing and release and finished product?

How should RDRC ensure protocols meet finished product testing, including radiochemical and radionuclidic purity; chemical purity; specific activity, if pertinent; sterility and pyrogen-free; adequacy of analytical procedures for finished product tests? For example, how should RDRC protocols ensure that analytical procedures are suitable for determining quantitative attributes

such as radiochemical purity, radionuclidic purity, chemical purity and mass, and capable of giving reliable results?

How should RDRC protocols ensure that analytical equipment is working properly at the time the test is performed and is calibrated for assurance that the test results are reliable? Thanks very much.

RDRC and the Safety of Women of Childbearing Potential

DR. LOEWKE: Good afternoon. Hi. I am Sally Loewke, the Deputy Director for the Division of Medical Imaging and radiopharmaceutical Drug Products.

This afternoon I would like to introduce the topic of the safety of women of childbearing potential under RDRC. Under the regulation it states, each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before she may participate in the study.

Whether being studied under IND or RDRC, there is an obligation of the investigator to ensure that a female is not pregnant. Under RDRC, the issue of pharmacologic effect is not a common concern for the adult female. However, if she is unknowingly pregnant the risks of pharmacological effect and radiation risk to the fetus are of concern.

Under the RDRC regulations, it basically allows for confirmation of the non-pregnant status as either a written statement or pregnancy test. What the regulation does not clarify is what information is collected from the patient that would make the investigator comfortable with a written statement alone, i.e., are we looking and verifying whether or not the patient is on contraception, the timing and type, the last menstrual period, whether the patient is post-menopausal, or by history had tubal ligation or a hysterectomy. And, the regulation does not specifically identify whether a urine or serum pregnancy test needs to be done.

Typically, under IND, just for some sake of comparison I have thrown this slide up to show that with IND drugs we may have a pharmacologic effect and usually this is first-in-human studies. So, it is important that non-pregnant status be confirmed, and it is usually done either by testing or a history of the patient being post-menopausal or history of tubal ligation or hysterectomy. Often, if not in most cases, pregnancy testing is usually within 24 hours of drug administration. I don't think there is any one standard for any particular IND. I think it is probably on a case-by-case basis whether or not urine or serum pregnancy testing is required.

So, basically, to get the discussion rolling we proposed this question in the FR notice, is written attestation adequate assurance that female research subjects are not pregnant? If not, what other assurance should be provided?

I would like to introduce our next speaker, Cpt. Rich Fejka. He will be speaking on membership and administrative issues.

RDRC: Membership and Administrative Issues

CPT. FEJKA: Thank you and good afternoon. The FDA has been reexamining 21 CFR 361.1, regs which govern the actions of the radioactive drug research committee. My presentation will cover membership and administrative issues.

The following is presented to refresh your memories as to the specific membership requirements for a committee. 21 CFR 361.1(c)(1), membership, states a radioactive drug research committee shall consist of at least five individuals. Each committee shall include the following three individuals, a physician recognized as a specialist in nuclear medicine, a person qualified by training and experience to formulate radioactive drugs, and a person with special competence in radiation safety and radiation dosimetry.

So, membership issue number one relates to the responsibility of the committee to assess the proposed pharmacological dose in the study. 21 CFR 361.1.(b)(2), limit on pharmacological dose, states the amount of active ingredient or combination of

active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.

And, in (d)(2), pharmacological dosage, states to determine that the amount of active ingredient to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

So, our questions are would an RDRC benefit from additional expertise such as a from a pharmacologist or toxicologist?

Two, should FDA require a member with specific expertise to determine that the proposed pharmacological dose does not cause a clinically detectable effect?

Now, if it is decided to add a pharmacologist to the required defined membership, then based upon the reg found in (c)(2), function, which states each committee shall meet at least

once each quarter in which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present with appropriate representation of the required fields of specialization. So, realize if the addition of another required member is acceptable, then the minimum number of committee members will increase from five to seven, and we are seeking your comments on this issue.

A second membership issue is as it relates to the reaction drug formulator and the responsibility of the committee to assure the quality of the radioactive drug. So, 21 CFR 361.1(c)(1), membership, second section, requires each committee to include a person qualified by training and experience to formulate radioactive drugs.

(d)(6) states the quality of the radioactive drug addresses the expectation of the RDRC to assure appropriate and reproducible drug quality, and to determine that the radioactive materials for parenteral use are prepared in a

sterile and pyrogen-free form.

(d)(7), the research protocol, requires the RDRC review a protocol which is to address all requirements of Section (d).

So, our questions are should the member qualified by training and experience to formulate radioactive drugs, who undertakes the review specified in (d)(6), as required in (d)(7), should it be more explicitly defined, for example, a nuclear pharmacist or a chemist or a nuclear medicine technologist?

Two, what level of training and experience is necessary for this member to possess?

Now I would like to address some of the administrative issues. Administrative issue one relates to changes in committee membership. 21 CFR 361.1 (c)(4), approval states, changes in membership and applications for new members shall be submitted to the FDA as soon as or before a vacancies occur on the committee. Now, FDA is concerned that unqualified members may be serving on an RDRC and as a result of untimely notification

to FDA of changes in committee membership.

So, our question is should the regulations specifically require that FDA approve RDRC membership changes before new members assume committee responsibilities?

The second administrative issue relates to withdrawal of a committee's approval. Now, (c)(4), approval states, approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section. Approval of a committee shall remain effective unless and until the FDA withdraws such approval.

So, our question to you is what level of non-compliance of an RDRC should necessitate FDA to withdraw a committee's approval for their failure to comply with any of the requirements of 21 CFR 361.1?

The final administrative issue is more of a housekeeping matter and relates to what I will call an inactive status of a committee. FDA has allowed a committee to be placed on inactive

status, which is not required to submit an annual report, upon their request. FDA is proposing to amend the regulations to allow this. We seek your comments on this issue. That is it for me. Thanks.

Public Presentations

DR. MILLS: We have three public speakers before the break, Dr. Royal, Dr. Thakur and Dr. Beven. Dr. Royal?

DR. ROYAL: I am going to address the issue of pregnancy test to exclude pregnant women from research. Basically, I am going to talk about radiation risk during pregnancy. It seems to me that the need for a pregnancy test should be somehow tied to the magnitude of the risk although, I must admit, one of the things that has been bothering me at this meeting is the concept that there is no amount of radiation that represents a minimal risk. So, I would like you to believe that the risk from radiation is related to the dose, and the smaller the dose the smaller the risk. So, there should be a minimum amount of radiation that

is associated with minimal risk.

Then I want to talk a little bit about pregnancy test and then about mutagenesis, what women should be told after being exposed to radiation in terms of whether or not they should or should not become pregnant.

So, in terms of radiation effects in pregnancy, the effects depend on the dose, and it depends on when in gestation the radiation occurred. An important thing to remember is that congenital abnormalities, teratogenic effects or really deterministic effects--you don't get a teratogenic effect from radiation by affecting a single cell. Really the biological mechanism behind it is affecting many cells. And the one thing that is a stochastic effect is childhood cancer.

So, what do we know about radiation in pregnancy? Well, here are some graphs from the atomic bomb survivors. When they looked at field dose versus severe mental retardation, you can see the incidence versus dose. These doses are in Gray

so that 0.5 is 50 rem. It is pretty clear from the atomic bomb survivor study that the risk is greatest between 8 and 15 weeks. Risk was also seen between 16 and 25 weeks, but below 8 weeks and above 25 weeks there was no increased risk in severe mental retardation.

If you look at a more subtle indicator of risk by decrease in IQ score, you can see from this graph that things more or less follow the same pattern. Here we have time when in gestation of the radiation dose occurred. Then, these different colored bars represent the radiation dose. So, you can see that there is not a statistically significant decrease in IQ during 0-7 weeks, nor 26 weeks-plus, but when you look at 8-15 weeks and 16-25 weeks there is a statistically significant difference with doses over 50 rems.

In summary, in terms of teratogenic effects, mental retardation in the atomic bomb survivors, anyway, has been the greatest effect. That was an incidence of about 0.4 percent per rem but it is likely that there is a threshold at 20-40

rems. In terms of decreasing IQ, it was about 0.3 units per rem but, again, likely that there was a threshold.

As I mentioned, the real concern with radiation exposure during pregnancy at low doses is childhood cancer and this slide lists some risk estimates. It is somewhat controversial because studies that were done a long time ago, which indicated a rather significant risk of childhood cancer, those same sorts of risks were not seen in the atomic bomb survivors. So, it is still somewhat controversial but I don't think there is any doubt that the main concern about exposure at low doses during pregnancy is the stochastic effect, that is, childhood cancer.

One of the things that I just wanted to remind everyone is that pregnancy is a risky business and that 4-5 percent of all pregnancies have some bad outcome. So, that is another problem that we have to deal with. If someone is exposed to radiation, is it the radiation or some other thing that has caused the bad outcome?

In terms of pregnancy testing, given that the risk is small with fetal doses in a few hundred millirem range, written attestation should suffice. That is actually what we do in the clinical practice of medicine. We don't generally do pregnancy tests in people who are going to be exposed to a few hundred millirems.

I would point out that people living in different parts of the United States, during their pregnancy, they may be exposed to certainly 100 millirems more during their pregnancy, depending on where they live, and that this is really a small risk. For fetal doses greater than a rem, a pregnancy test might be prudent. Pregnancy tests certainly are easy to do. My concern about doing something different in research than we do in clinical practice is that it conveys the idea to the patient that the research somehow represents a bigger risk during pregnancy than if we were doing a clinical test. So, that is the disadvantage of doing a pregnancy test in everyone.

The last thing I wanted to talk about is

mutagenesis. This is what happens if you are exposed to radiation and then subsequently become pregnant. Certainly, it would be very obvious that if you look at somatic cells there are chromosomal abnormalities but what we are talking about here is chromosomal abnormalities in germ cells. Again, if you look at the results of the atomic bomb survivor study, there were about 38,000 parents who subsequently had 75,000 children, and if you look to find significant differences, there were none.

You can look at protein electrophoresis in order to look for protein abnormalities that might not be expressed phenotypically and, again, there were no significant differences.

BEIR V concluded that mutagenesis had not been demonstrated in humans, even though there is abundant evidence in some plants and animals that you have mutagenesis at high doses. So, as you heard this morning, the weighting factor for the gonadal dose is decreasing quite a bit and it is because the more we have studied the effects of radiation, the less and less have we become

concerned about mutagenic effects in humans.

Well, this has some practical implications in terms of doing research and also in the clinical practice of medicine about what you should tell a woman, who has been exposed to radiation, in terms of delaying her pregnancy.

This slide is the relationship between genetic effects and maternal age, so having nothing to do with radiation. You can see that once you get to be about the age of 35 there is a significant increase in genetic effects. So, certainly, one of the things that troubles me is to hear people tell women, after having been exposed to radiation, that they should wait six months to become pregnant, especially if they are 35 years old because basically we are telling them to trade the immeasurable effect from radiation exposure for a very real effect related to maternal age.

So, my conclusion about mutagenic effects is that it really has been an immeasurable risk in humans, and pregnancy really should be delayed only if it is expected that the health of the mother

will improve with time. Thank you.

DR. MILLS: Thank you, Dr. Royal. Dr. Thakur?

DR. THAKUR: Thank you, Dr. Mills. What I am going to do is briefly state to you what the Society of Nuclear Medicine is, what we stand for, and then make perhaps a couple of suggestions on the composition of an RDRC.

The Society of Nuclear Medicine was formed 50 years ago, in 1954. The mission of the Society is to promote the science and technology of the clinical applications of nuclear medicine. We have about 15,000 members, composed of physicians, technologists and scientists specialized in research and practice of nuclear medicine.

Consistent with its goals, the Society publishes periodicals, newsletters, books, and sponsors national and international symposia meetings that promote the practices of nuclear medicine, as well as the advances in technology and medicine.

SNM supports RDRC and recognizes RDRC's

contribution to both nuclear medicine and to the approximately 16 million patients that it serves each year. SNM welcomes all the opportunities to work with the staff of FDA to enhance the function and effectiveness of RDRC.

SNM believes that RDRC benefits greatly from the current 21 CFR 361.1(c)(1) requirement that is comprised of the nuclear medicine physician, the person qualified to formulate radioactive drugs and a person who is specialized in radiation safety and radiation dosimetry calculations.

We also believe that RDRC will greatly benefit by including a pharmacologist in its composition, and we believe that because we think that a pharmacologist will better advise RDRC of the in vivo interaction of a radiopharmaceutical or a molecular probe when it is administered in a minute quantity, and I think that should be the important function in this consideration.

SNM suggests that at the time of change in RDRC membership or recruiting a new member, RDRC

chair should submit to FDA the qualification, that is, a c.v. and the role of this member in RDRC. FDA then shall review the qualification of the proposed RDRC member and make its recommendation within 30 days after receiving those applications. RDRC then can act on the status of that proposed member. Those are the suggestions. Thank you.

DR. MILLS: Dr. Thakur, thank you. Dr. Beven?

DR. BEVEN: Thank you, Dr. Mills. This is going to be a group of "me too" remarks following Dr. Thakur's presentation. I am presenting these remarks on behalf of the American College of Nuclear Physicians.

For your information, the ACNP is comprised of physicians and others dedicated to enhancing the practice or nuclear medicine through study, education and importance of clinical practices. It was founded in 1974. ACNP is a trade association devoted to looking after the social and economic interests of those involved in nuclear medicine practice, and we are designed to

interact with legislative bodies, regulatory bodies, the media, the public and other professional organizations.

The ACNP supports the RDRC and recognizes RDRC's contributions to both nuclear medicine physicians and the patients that we serve. The College welcomes any opportunity to work more closely with the FDA staff to improve the function and effectiveness of the RDRC.

ACNP believe the RDRC benefits greatly from the current requirements that it be comprised of a nuclear medicine physician, a person qualified to formulate radioactive drugs and a person with special competency in radiation safety and radiation dosimetry.

ACNP believes that the RDRC would benefit by including a pharmacologist and a nuclear medicine physician with substantial experience in PET and PET-CT. The rationale for the pharmacologist, as stated by Dr. Thakur, would be to provide expertise on the in vivo actions of drugs when used in very small quantities, if any

such actions exist.

The rationale for including a nuclear medicine physician with experience in PET and PET-CT is the number of RDRC protocols which are presently active which indicate the interest in employing RDRCs in the area of PET research.

We do believe that it would be better to have FDA approve RDRC staff changes because the work may be disrupted if unqualified individuals or individuals deemed unqualified by FDA were appointed and removed after the fact. We further believe it would be better to have changes reviewed jointly by FDA staff and representatives of provider interest, such as ACNP and SNM. This would just avoid misunderstandings about the qualifications of prospective members. We envision that the replacement system would work as follows, that the RDRC would provide a c.v. of the proposed member. The FDA staff would review the qualifications, notify the RDRC of its decision within 30 days, and the RDRC would act on the status of the proposed member. This concludes my

remarks.

DR. MILLS: Thank you, Dr. Beven. We are moving through the afternoon rather quickly. Is Dr. Smith available? Would you like to come now? We will have your presentation and we will continue on through until 2:30 and then, if everyone has concluded before then, we will break. If not, we will have speakers that follow the break.

DR. SMITH: Thank you. I would like to address the issue of biologics review by RDRC. We have heard twice today that monoclonal antibodies are not subject to RDRC review because of the potential for biological response. Indeed, in a recent request for guidance from the FDA and CDER on a project that we tried to review for RDRC approval of monoclonal antibody, that was declined due to the fact that the monoclonal antibody is capable of eliciting a biological response.

That guidance went on to say all radioactive biologicals may elicit biological responses and, therefore, are inappropriate for the RDRC mechanism. That is despite the fact that the

RDRC definition of a drug includes biologicals under 21 CFR 3(100). I believe that, because of this position taken by the CDER and FDA, it is necessary then to file an IND for all biological agents and, considering the rapid pace of development in this area, I believe that that really hinders the development of new radiopharmaceutical agents that are biological agents.

As evidence of this, we have mentioned today Zevolin and I can think of Capromal as the only agents that I can think of as monoclonal antibodies that are available for diagnostic or therapeutic work despite the compendium of thousands of agents used in research laboratories around the country and the world.

So, I would propose or probably more accurately request that the FDA consider giving authority to local RDRCs to approve biologics for clinical research studies.

21 CFR 3(10)(n) states that the radioactive drug includes a radioactive biological

product as defined in 21 CFR 600.3(ee). That, in turn, specifies a biological product which is labeled with a radionuclide.

Biologics regulated by the CBER under the FDA, and this comes straight from their site which defines biological products, includes monoclonal antibodies for in vivo use, and includes other proteins like cytokines, enzymes and other novel proteins, immunomodulators, growth factors and other monoclonal antibodies intended to mobilize hematopoietic system cells, cellular products, vaccines, allogeneic extracts, antitoxins and antivenins, and blood component products. All of these are considered under the definition of biologics by CBER.

Now, as with conventional drugs, typically monoclonal antibody studies for use under RDRC are given in small doses compared to those used for therapy purposes. As an example, in our study that was declined we were looking to using 1 mg of antibody. That compares to a treatment dose, for example for Rituxan of approximately 650 mg or 2-3

orders of magnitude lower dose for the RDRC request. For Bexar, the total amount of antibody given to the patient is 485 mg given twice for almost 1000 mg of antibody, so again an order of magnitude of 3 lower than typical therapy antibody.

As with any drug, there are risks of side effects or allergic reactions, but I would not consider an allergic reaction which can occur with any drug to be the same as a pharmacologic effect, and those can be mediated, with respect to biological agents, by the administration of acetaminophen and other antihistamine agents.

In conclusion, the regulations currently provide for biological agents to be approved under RDRC regulations as I have mentioned. So, unlike some of the issues discussed today, I don't believe that this requires a new set of regulations to be approved but simply I would request guidance or guidelines from the FDA on how to be able to establish a mechanism whereby RDRCs could approve and oversee the use of biologic agents for clinical research. Thank you.

DR. MILLS: Thank you, Dr. Smith. Dr. Garner?

DR. GARNER: Good afternoon everyone, and thank you for allowing me to be here. I am probably the only non-American speaker for the whole day and you might feel it a little presumptuous of me, therefore, to be telling you what I think you ought to be doing but I will do that nevertheless.

What I am going to talk about is a concept which has really evolved from a technology, and it is described as the microdose concept. Perhaps setting the scene for this, I think the FDA's Critical Path document is an excellent document which has certainly caused lots of discussion both within the academic community and within both industry and regulatory authorities. Of course, the issue with the Critical Path document is now to translate what are in totality generalities to actual specifics, and I believe the RDRC regulation that you have here may be a way of actually improving the way that we develop drugs.

So, within that document it states that a new product development tool kit is urgently needed to improve predictability, and we have heard today about some of the newer imaging technologies that might be able to expedite this, and I am going to talk about an additional technology which hasn't been so far mentioned today, and that is called accelerated mass spectrometry.

I am sure you are all familiar in terms of drug development that one of the requirements when you are studying new drugs is to understand their metabolism which, of course, is one of the criteria within the RDRC regulation. The reasons for drug failure may often lie, indeed, with suboptimal metabolism or suboptimal pharmacokinetics. Although we can have a debate about what the percentage is that relates to that, there is no doubt that incorrect metabolism is a factor in drug failure. Indeed, if you talk to industry representatives, varying from company to company, you can see that as much as one in three molecules may have some metabolism issues.

Now, here we are today with genomics, proteomics, identifying many new targets and, as a result, we have many new candidate drugs coming forward. The issue is how can we take these candidate drugs forward into humans with, if you like, the least regulatory steer. Can we take these into humans with minimal toxicology? Can we use that information to deroute these molecules in order then to know which ones to take forward for what I would call conventional drug development testing?

So, the AMS technology--I show you here a picture of two instruments. The one on the left is an instrument that has been around for 20-30 years and you can see that is a rather large piece. In fact, that room is about the size of two tennis courts. Whereas, the instrument here, on the right-hand side, is a much smaller AMS instrument. This instrument is likely to be the future for biomedical applications of this technology.

Now, what do these instruments do? Well, basically what they do is they measure elemental

isotopes at the single atom level. So, about half the elements in the periodic table can actually be analyzed using this technology. I am going to focus pretty much on the use of AMS for the measurement of 14-carbon. The reason, of course, is that 14-carbon is the isotope really of most use when it comes to labeling biological molecules or small organic molecules.

The data that comes out of these instruments is not a radioactivity measurement since, as I say, we are counting atoms but we always express the data in radioactive units of one sort or another. The interesting thing about the technology is that, provided we can build the 14-carbon into a molecule, we can measure the fate of the molecule in humans, and those molecules can be drugs; they can be metabolites, proteins, peptides and endogenous molecules. So, here we have a means of studying what happens to these molecules in the human body.

The issues, of course, are whether the current RDRC regulation might permit use of labeled

molecules in a way that I am going to describe in a moment. So, with the technology we can measure down to extremely levels of drug substance, in the attogram to zeptogram range. This is of the 14-carbon atoms themselves. What that means in reality is that we can administer, and be able to trace within the human subject, within the human body, very low levels of C-14. As I mentioned, the instrument actually measures the natural background in terms of atoms. So, it is that sensitivity that allows us to do these microdosing and ultra low labeled studies.

So, just to put things into context for those of you who do labeled studies, and I apologize for using old units as opposed to SI units, but I am still too old to understand what a Becquerel is. The 80-100 microcuries is a typical dose for a standard radiolabeled study and, of course, that radioactive dose is quite substantial. It depends on the radiation exposure within the body as to what the radiation dose truly is. However, for these AMS type studies we can move

from the microcuries to the nanocuries. Typically, we can use as little as 100 nanocurie doses per person so we have reduced that radioactive exposure by 1000-fold. So, if there is a linear relationship between exposure and biological damage, then we have reduced the biological damage hazard by 1000-fold as well.

So, just to put also what I am going to talk about in context, we actually contain--I haven't heard this mentioned today, but we contain about 400 nanocuries of 14-carbon in our bodies. In other words, we are irradiating ourselves all the time because of the carbon cycle and the fact that we ingest 14-carbon. So, put that into context. That is the dose one would administer for these types of studies.

We also contain a fair amount of potassium-40 and, just to put things into context, the banana contains about 1 nanocurie of potassium-40. So, what we are saying is that for this type of study, these metabolism studies, we are administering 100 bananas worth of

radioactivity to a person. In other words, it is really of no consequence from a risk perspective and that is obviously an issue that I want to raise in a moment.

So, the question is, is there a de minimis level of 14-carbon that can be administered to humans in the U.S. without animal dosimetry under this regulation? Can we administer 50 nanocuries, 100 nanocuries, 1 nanocurie? Because using the technology we can certainly measure our molecules under those very, very low doses. And, to me, it is a bit nonsensical to be having to do animal dosimetry studies when the dose is really at a background level.

So, what is microdosing? Well, it is a way of getting some early read on human metabolism, as I mentioned, and with minimal preclinical toxicology. Clearly, in a microdose study--and this is independent of the RDRC, it states that no pharmacological or toxic effect should be manifest. That is in the human subjects. And, from these types of studies we don't get any information about

human safety or efficacy. We are looking only at the metabolism and clearance of our molecule from the body. We need ultra-sensitive procedures. We have heard already something about PET. AMS is another ultra-sensitive big physics technology which allows us to do these microdose studies.

So, in terms of what the problem is, it is the lack of predictivity of animal models. That is the problem that we have today. That is one of the reasons that drugs are failing down the development path because humans are not rats or mice or dogs or monkeys. We all handle drugs in our own often unique way.

So, the current regulatory position, as you know, in relation to this regulation is, is the agency minded to update this regulation to include NCEs? What is a microdose? Well, actually in Europe we have a regulation already in place, or a guidance document in place as we have heard earlier today. It defines the microdose as 100th of the pharmacological dose, based on animal data or in vitro systems, in other words, it is animal or in

vitro, to define the dose but the maximum dose we can administer is 100 mcg. So, again, should this regulation include specific mention of microdosing as per the EMEA definition?

I haven't got time to cover the preclinical testing that has been defined in Europe, but let me just say it is a very simple package in a single species, namely rats, and a bit of cardiovascular safety.

So, again, what preclinical tox package could be used to support microdosing studies if, indeed, it was minded that this regulation would allow these microdose studies because, after all, we are talking about the same type of study as with a PET ligand.

So, the regulatory issues really to be considered are can this regulation cover microdose studies? Is the AMS technology going to be useful within that context? I just would clearly point out also that under the LARA principle these radioactive doses are more acceptable than what we are doing currently. Finally, should we be using

these microdosing procedures as the first-in-human studies rather than the current Phase I studies? Thank you for your attention.

DR. MILLS: Dr. Garner, thank you. Dr. Chansler?

DR. CHANSLER: Hi. My name is Michael Chansler and I represent Accium BioSciences, an industry contract research organization. I want to echo Dr. Garner's thoughts and concerns for microdosing in first-in-human studies using the technology of AMS.

My background is in biology and nutrition, specifically looking at bioavailability of micronutrients. I left the academia world about 15 years ago and I have been doing marketing and business development in instrumentation, and also moved into the contract research services area. So, as I move forward you will hear a little bit of marketing, a little different than you heard before.

Now, I attended the American Pharmaceutical Society's meeting last week and

there was an open forum on opportunities and challenge in modern bioanalysis. Someone from the FDA, Dr. Bryan Booth from the CDER group, was there and there was a discussion about AMS and some of these regulations, and he took a few arrows for you, guys, there and there was as well a very lively discussion by bioanalysts. What we are looking at, as opposed to looking at the nuclear medicine side of things, this is more of a bioanalytical technique that is new to the area.

So, Accium is a company, starting in Seattle. We are focusing our key expertise on Phase 0 and Phase I clinical trials and technologies, as with accelerated mass spectrometry, LCS, MS and some pharmacogenomics, and we will specialize in low radiation mass balance studies, metabolite profiling and the absolute bioavailability, as well as microdosing.

So, in the last 10, 20 years there has been a whole bunch of new technologies that have come out that have really helped industry get a lot of candidates out there. We have been able to

identify thousands of new potential targets using genomic technologies. Combinatorial chemistry technologies have given us hundreds of thousands of new compounds that we get to work with. Then, high throughput screening has, you know, helped us identify hundreds of new drug candidates. But we still have a problem here because we are spending a lot of money to develop these new drugs and, as time goes by, we are getting less drugs passed through to industry. So, there is a certain area here where there is a key focus in the drug development process and, industry, you have your laboratory research to into animal studies and then into the following Phase I, II, III clinical trials work.

About 30-40 percent of the drugs fail due to poor performance. Whether that is toxicogenomics, PK or bioavailability, they fail right there in the animal-human transition. Some of the key points are, as Dr. Garner pointed out, are the in vitro and animal models are very poor predictors of bioavailability. It is very hard to

get any kind of PK predictions from animal models. Therefore, it is very hard to set starting dosage rates when they go into the clinic.

So, one of the ideas on how we can decrease that is to help researchers and drug developers make better candidate selections earlier in the drug development process, and one of those is this microdosing technique, as Dr. Garner described.

He described AMS as very sensitive for measuring C-14 compounds. It is about 1000 times more sensitive than the best mass specs that are out there now. The biological applications were developed at Lawrence Livermore Laboratories, and many of the top drug companies have verified that AMS is a valuable tool for doing microdosing and some of these other studies. As already described, a microdose is 100th of expected therapeutic dose. It is one of these emerging and generally accepted definitions, up to 100 mcg of the drug. And, the test compound can have no pharmacological effect.

So, what microdosing can do is help the

drug companies with candidate selection. You know, they may have four or five compounds. They don't know which ones to take to the clinic and it costs a lot of money to do the tox. So, getting early PK data will help out there. There is low radiation exposure, as Dr. Garner said, about 100 nanocuries of radiation and that is less than I got flying here from Seattle on the airplane.

So, there really isn't a radiation risk of this technology. There is a reduced development time. You know, we can get from candidate to actually PK data in less than three months and reduce cost for the drug industry by preparing 100 g of a test compound as opposed to kilograms to get into tests.

So, this is all great and it is fantastic. Why isn't it being used here, in the U.S.? Well, there has been no access to AMS instrumentation. There are no GLP compliant labs for them. There are no dedicated clinical facilities that are designed for low carbon-14 dose delivery and sample collection, and there are some issues with CFR

361.1 regulations.

So, we have taken care of the first two but there are still some regulatory issues. First and foremost, I believe that all the regulations are set up for the ethical demands for safety and efficacy to our patients, to our subjects and our testing. I guess one of the key questions is, is there different safety information that is appropriate for different stages of the drug development process? In particular for first-in-human studies efficacy is not an issue. I am looking for PK only so really the issue that we are looking at is safety in that area. Then, how much is an investigator expected to know to do one of these studies?

In the U.S. we have issues with those. In Europe there are these EMEA guidelines that were talked about this morning that support some non-clinical safety studies, that will support a single microdose study in humans that will allow us to get these. So, there is some information out there. It is accepted. There is guidance in

Europe, not here in the U.S. It came into play in July of 2003. Specific non-clinical safety studies are required to support these studies. It describes that microdosing is really mostly for internal PK analysis of compounds and the document has streamlined the regulatory pathway. There is a tox package that was talked about by Dr. Garner.

Our recommendations or our thoughts are for changing these regulations for bioanalysis. I don't know how pertinent it is to nuclear imaging and medical imaging but I believe that the EMEA has given reasonable guidance for characterization of PK and ADME in these microdosing studies, and there are a couple of options that we can work with there. One is to change 361.1 to allow first-in-humans testing. That would entail getting some guidance on specific non-clinical safety studies required to support a single microdosing study because I believe, you know, there are different types of safety requirements for different stages in the drug development process.

The other is to look at this exploratory

IND, and I stress the word simplified process because this technique is going to be very important for the smaller biotech companies which really, you know, look at their pocketbook as they move forward and this will allow them to get into clinical trials quicker with good medications. Thank you.

DR. MILLS: Dr. Chansler, thank you. It is 2:30. We will go on a break for 15 minutes and then we will come back for Dr. Taylor's presentation and then we will go to the open microphone. Thank you.

[Brief recess]

DR. MILLS: Let's start again and we will have Dr. Taylor up here in just a moment.

DR. TAYLOR: I want to thank the FDA for actually having this session and giving us a chance to provide some input. I am Co-Director of Nuclear Medicine at Emory. I have been past chair of the American Board of Nuclear Medicine. But I also like to think of myself as just a member of the general public, and a member of the aging general

public who would like to bring these new developments in medicine from the laboratory to the bedside as expeditiously as possible before I need them and perhaps reduce cost.

As you can see from this slide, I made it before the election but both President Bush and Senator Kerry really had an emphasis on trying to reduce drug costs, and I think the RDRC has in the past played an important role in facilitating translational research and can minimize the growth of healthcare cost.

I wanted just to give a persona example of that from my own experience. The rules were enacted in 1975 but perhaps the interpretation of the rules was a little more liberal. But at that time, at least the RDRC at the University of Utah allowed first-in-man studies, probably under the assumption that tracer doses are too low to have a toxic or pharmacologic effect, and often the tracer was chemically similar to a drug or a class of drugs that were already known to be safe in man.

As a specific example, I was working with

Alan Fritzberg at the University of Utah, and Alan had synthesized several potential new agents which looked very good in rats, but the question was are they going to work in humans? These are four of the agents. We applied to the RDRC to test all of these agents in humans to study biodistribution, clearance. Only MAG-3 really functioned well in humans so, based on that, we eliminated the other studies. We subsequently got an IND for MAG-3 and subsequently Mallinckrodt took it over and made a commercial drug out of it.

I am sure you are aware of this but I just wanted to reemphasize that when we got our IND at the University of Utah we had to perform toxicity studies in rats, and we had to synthesize quite a lot of MAG-3. But, in fact, you can't perform a toxicity study with a technetium complex because technetium-99m has too short a half-life. Tech-99 can't be obtained in sufficient quantities for toxicity studies. I think it took about 400 mg/kg for us to kill a rat with MAG-3. Even if we could obtain tech-99 for toxicity studies, we would have

to keep it in our refrigerators far into the future because of its radiation safety issues.

So, I think it is important to distinguish the ligand and toxicity, which we prepared and we tested the ligand but, actually, for the studies that we did under the RDRC we separated the ligand from the complex. We didn't inject the ligand into the patients. So, the toxicity studies we did with the ligand were subsequently relevant for Mallinckrodt but weren't relevant for what we were doing with the RDRC. We were only injecting the complex. Again, with HPLC purification one can potentially develop the conditions that separate the complex from the ligand so for RDRCs we are only dealing with the complex.

We looked at the volume of material that we give, and for 10 millicuries of MAG-3 it is about a tenth of a nanogram. Bacterial toxins resemble enzymes and they are evolved catalytically and exhibit some specificity. But if one were trying to develop an agent that was quite toxic, and if one compared it with a plant toxin, then

looking at, say, ricin or aflatoxin or strychnine the dose to produce a toxic effect or lethal effect is 7000 to two million nanograms per kilogram, whereas we were giving MAG-3 at 10 millicuries. Again, this is an HPLC purified MAG-3; it does not contain the ligand. The dose is much less. So, I think that there is a tremendous safety margin.

So, what I would like to request is that the RDRC should be permitted to continue to allow studies, particularly first-in-man studies with technetium complexes because they can only be administered in tracer doses because of physical constraints, and one cannot perform toxicity studies with a technetium complex, only with the ligand. Comparing it to plant proteins that are known to be toxic, there is a safety factor of 1000 to a million.

This type of approach I think will facilitate translational research and reduce the cost of drug development. Similarly, I think for other agents, non-technetium agents, for example, one could make a cold fluorine compound and then

perform toxicity studies but if one is really using tiny, tiny doses and it has a structure similar to agents that are known to be safe in man, I would like to see the RDRCs to continue to have the authority to evaluate those studies on a case-by-case basis or study-by-study basis and to approve them. Thank you very much.

DR. MILLS: Thank you, Dr. Taylor. We have concluded with the scheduled speakers and now we are going to have the open public microphone. This room and this meeting will continue until 4:30 so we will have that much time to add comments.

Certainly, this afternoon we have heard presentations and the open public microphone is available for comments about what we heard this afternoon, as well as what we heard about this morning. So, I want everyone to realize that it is not limited to just this afternoon. I think the most important message that I can give, and I will emphasize this again at the conclusion again, is the fact that this isn't the end of this public comment. We have another 60 days for that open

public comment coming to the docket, and I anticipate that there will be a lot of cross-fertilization, a lot of focusing of thoughts and processes, and the more that you can put together and give us in that open public forum to the docket, that input is going to be of great value in terms of the development of the RDRC. So, please, share with us your thoughts. Also remember that everybody that you have seen up here is going to read all of those comments so make them concise. When you start to get real wordy, remember I have to read them all. Okay? And, I will read them all so make your message clear and clean for me. I would appreciate it. So, the microphone is open.

DR. CONTI: Peter Conti, President Elect of the Society of Nuclear Medicine. I am a professor of radiology at the University of Southern California--so, number one football team of the country, by the way, just in case anybody missed that. I apologize to the Auburn and the Oklahoma fans.

[Laughter]

The comment that I have is just very brief, and I will come back to the microphone after giving some other folks a chance, but I am concerned about the timeline on the comment period with the January 16 deadline, given the fact that we are going into the holiday seasons and the likelihood of the FDA or me doing anything in the next few months is going to be limited, but also with respect to the release of an actual product with respect to these exploratory of expedited INDs. Without that material in hand, I don't believe we can make substantive comments on this process because it may have an impact on what is written. So, my suggestion is to consider that the date be set at the release of the first draft of the exploratory INDs.

DR. MILLS: And certainly that may be one of the first comments to submit into the docket in terms of the time frame element you have just identified. Being involved, indeed, in the other process also, we anticipate that will come out as a draft guidance which will have its own docket and

its own informational flow. We are sensitive to the crossover between these two and the understanding of the interface between those. So, I anticipate that much of the docket that I am going to read for RDRC I will be reading at the same time for the exploratory IND. So, I certainly would be sensitive to the concern that we are closing comments too early, and certainly that would be one of the things that you might want to put in now, especially when you have identified that there is another crossing guidance that is going to be coming out from FDA which would necessarily influence your comments.

DR. INNIS: Bob Innis, from NIH. I have two comments, one having to deal with sort of policy or politics, and the other a question about actual implementation of any changes to RDRC.

I am wondering, with regard to policy and politics, if this might not be a good time--and I don't know specifically how to do it--to try to have an alliance between NIH and the FDA and possibly also industry to advocate some changes.

Because of the policy at FDA which we have heard about of the Critical Path, which has identified imaging agents as being one to enhance--an important critical path to enhance bringing therapeutic drugs to market.

Also, there is a very similar policy, or whatever, at NIH, for people who don't know it called the Roadmap, the brain child of Dr. Zerhouni who is the head of NIH. There, they are looking for critical paths, rate-limiting steps for research to be translated from the bench to the bedside. So, it is very similar and some of the terms are kind of similar.

An example is that one of the specific roadmaps is around the development of probes to be used in vitro and in vivo. So, there is a strong interest and if there is a similar policy at FDA it might be an appropriate time at some high levels, or maybe there is already, for an orientation to try to do that.

I really appreciate this meeting that the FDA held today. I feel it is very refreshing

relative to the contacts I have had in prior years with the radiopharmaceutical section at the FDA. There is a lot more clarity and there is an openness for considering the important research issues, for considering decreasing the barriers, that I just haven't seen before. So, I really appreciate that and if there is some way that NIH and the FDA could work towards that politically I would be very glad to support it. I can also say, vis-a-vis industry, one of the roadmap jargons now is public-private partnership so there is a strong interest in trying to have industry partner with NIH on some of these goals. So, if there were ways, and I don't know exactly what they are, I would be glad to help out as much as I could from the NIH perspective.

The other general comment was how long will each of these processes take? I mean, I have been following the GMP guidelines for PET for a long time--you know, how many years and people have told me it is going to be issued soon and it just isn't. How long do you expect there to be

changes--I guess they would have to be in the regulations, for the RDRC? In comparison, can just the interpretation of an IND--could you immediately start doing essentially the same sort of things in an IND, and does that make more sense for the foreseeable future than changes in the RDRC regs for years to come?

DR. MILLS: A couple of comments. Jerry, do you want to address what we have been doing with NIH so far? Jerry and I have been participating but I will let Jerry focus the discussions from his perspective.

DR. COLLINS: At the top levels of the FDA and the NIH there has certainly been cross-talk between the Roadmap and the Critical Path. So, there is not a gap; there is not a competition. The overlap occurs at the end of the NIH Roadmap and the beginning of the FDA Critical Path. That is, NIH starts with discovery, generally pulls it through early Phase I to Phase IIA. FDA generally becomes involved at the beginning of human experience or very late in toxicology true

development and goes all the way through Phase III to postmarketing issues. So, there are parts that are specific to each institution and parts in the middle, and there are some bridges in both regards.

The Center for Devices and Radiological Health has partnered with the Imaging and Bioengineering Institute at NIH to form a joint imaging lab to look at a lot of the technology hardware platform related issues. That initiative was announced in between Zerhouni's announcement and the FDA's announcement. So, that is one thing at the hardware end.

In the personnel end we have spent more time with the Cancer Institute and have formed the task forces that I mentioned during my presentation this morning. We have had individual meetings with other parts and pieces of the NIH, but the tradition of both agencies is to be sort of fragmented within itself so it is hard to get your arms around either one of them. But I think if you look at George Mills' calendar since he took over the Division directorship, he has spent a lot of

time in his car going south on Rockville Pike to meet with various folks.

DR. MILLS: In terms of a lot of initiatives--we are talking about the RDRC today but the Critical Path gets mentioned many times, and part of that development is just what Jerry is pointing out, that we reach in for various pieces and parts from NIH at the present time, and a lot of that right now is with NCI in terms of developing our initiatives. We have been putting together from the FDA side a listing of all of the biomarker imaging studies that we have been able to find throughout our various INDs and various developmental steps that we have gone through. We are pushing that together. NIH, at the same time, is looking in a similar fashion. We are working with them in terms of the PET evaluations and initiatives, looking at how we can improve specificity and sensitivity findings to be able to support in that area, and also looking at certain investigational development areas, one of which is looking at volumetric determinations versus

cross-product evaluations for tumor response in our oncology studies. So, there are a number of cross-fittings between the two.

Now, a couple of things in terms of the timing issues that we are being asked about, when you start of doing a regulation basically everybody kind of blinks around here, and I can tell you I have been here about 12 years and I got to do one in about 13 months but that was under a congressional mandate and they told us exactly what to write, and it took us about that long. Realistically, if we are looking at a regulation people kind of mumble but then it is going to be two to three to maybe four years to write a reg and get it all the way done. It is just the process we go through.

We can write guidances and draft guidances much more quickly and you will see much more activity. I would anticipate that we may be seeing a draft guidance coming out to support RDRC. I would anticipate that you are going to certainly see a draft guidance rather shortly in terms of the

exploratory IND. There is a real question in everyone's mind as to what is the difference between a guidance and a draft guidance. Okay? Because we are thinking, we are telling what we are thinking and even in a finished guidance document we are telling you what we are thinking. So, recognize that your input on draft guidances is as important as anything that we do in terms of developing regulations because you are giving us input in terms of what we are thinking in minute to minute activities. Guidances are different than regulations. Regulations are "must." You must do this. It is a regulation. Guidances are this is what we think you should be doing and we are thinking together as we do it. So, recognize we can come much more quickly with guidances and many times we will evolve guidances with your input once, twice, three times. Many of you in this room have seen it as we did the medical imaging guidance document--many evolutions; many thoughts and many changes in the process. So, anticipate that you will see those guidances much more quickly.

DR. CONTI: I think this is a good starting point for my two additional comments in terms of a guidance document or at least draft guidance. I think it is essential that we take the opportunity to define minimal risk because, clearly, since it is not in the regulation it is only a recommendation essentially from the NHRPAC. This is a golden opportunity to look at the radiation safety risks and to categorize them in terms of not absolute but relative risks.

I wanted to engage a little bit in the discussion with the bioethics person that was here, but I think that it is very important that we start to look at reality versus theory and begin to apply this in practical clinical settings. Most likely the majority of the patients--patients now, not volunteers because these are people with disease that have obvious and known risk factors for dying or having a fair degree of morbidity--that there are relative risk factors for getting these studies as opposed to just the absolute addition of a single diagnostic study in most cases.

So, it is very important that we take the opportunity to define what we mean by minimal risk and whether that could be a starting point to then allow us to enter some of the other categories, like in the pediatric statutes where we are looking at is this minimal risk or not; is it greater than minimal risk or not, because if it is categorized as minimal risk then we actually could qualify to go down that pathway and our IRBs would have some clear guidance as to how to handle this material.

The other thing I want to bring up is this issue about clinical trials. In the RDRC--I think Florence made the comment earlier this morning about immediate attention to diagnostics, but as you read on it goes into a number of other words--and I probably need glasses, this is so small--the research is not intended for immediate therapeutic diagnostic or similar purposes. Then it goes on, or to determine the safety and effectiveness of the drug in humans for such purposes, i.e., to carry out a clinical trial.

These are all clinical trials. So, we

need to define what we mean by a clinical trial. I think it was mentioned earlier should this be Phase I/II trials? I mean, SNM's position is very clear. We believe this is a Phase I/Phase II clinical trial form. When you read this, it is true. I am not going to use this to make a clinical management decision in a patient for the purposes of treating that patient under RDRC. On the other hand, it is very likely I am going to have a protocol that might use an experimental drug as part of a larger research study to determine the next move in that particular protocol.

The patient has signed up for participation in a research study that also happens to involve a radioactive research drug. Therefore, the patient is not necessarily being managed clinically on the basis of that drug's information but it may have an effect on part of the research study. So, how do we define that? These are important parameters we need to get our arms around in order to clarify what we can and cannot do in this area.

So, I think those two definitions, minimal risk and clinical trials, need to be formulated and perhaps this can be done in the guidance document for interpretation purposes. Obviously, it also needs to be clarified what we are talking about. We are talking about technetium ligands. We are talking about fluorine isotopic substitutions versus elemental substitutions. We have to get some guidance on this because, clearly, as you say, it is a mixed situation. We can't continue to operate under that type of scenario. So, I think we can get some consensus from the community as to what should and should not be and that could be dealt with in the guidance as well.

DR. MILLS: Don't walk away from the microphone. Let me just interact with you a little bit here because, number one, I certainly agree with the concern about defining minimal risk. I think one of the elements that you need to focus on when you are giving us input is to recognize who is the subject population we are dealing with. From that standpoint, my concern and focus for you is,

remember, when we are dealing on the drug side versus the biologics. In biologics there were never any normal human volunteers. Okay? That was a given. On the drug side there are. So, when you are looking at minimal risk what you have to reflect on is how you are going to enroll and design your studies and how you are going to propose your risk definitions against those subject populations. We need that input because, indeed, if we are looking at normal human subjects, certainly our concern about minimal risk is far different than if we are dealing with an individual who has a very short life span and who is trying to contribute to a disease development process where we may find an effective therapy. I see those as significantly different.

When you are talking to us in the docket, tell us who you are talking about, your subjects, and then talk about your risk and how you would want us to define it.

DR. CONTI: Right. We, in fact, deal with this every month in radiation safety committees.

When a patient protocol comes through with additional x-ray technology or additional study involving ionizing radiation, whether it is radioactive materials or otherwise, we have to make an assessment is this patient population at significant risk that the intervention that is being proposed is minimal compared to what the risk is for that particular patient population. So, I think that is a critical decision pathway.

On the other hand, I will use DEXA as a good example. DEXA scans are prevalent. Everyone is using them. But in our committee we are looking very closely at is this a group of kids, as someone said, off the street that are being evaluated with DEXA scans with multiple examinations to learn something about a normal population? Well, I think that raises a little bit more of a flag, if you will, than the obese adolescent population, let's say, that probably needs to have that because there may or may not be other ways of getting information or it is an at risk population or a diseased population.

So, we have to be practical about how we apply this. Maybe again in the guidance we can say, well, look, if it is normals maybe this is the appropriate pathway; if it is an at risk, disease population this is an appropriate pathway--again, relative risk.

DR. MILLS: The next one that you commented on were clinical trials. Frankly, like everybody in this room, we are a lot smarter in 2004 than we were in 1975. When we look at that input we need to understand your perspective on clinical trials and the input as to how you feel they should be defined in 2004 versus the well-intended statement in 1975. Twenty-nine years ago clinical trials had a much more generic and basic definition than what we have today.

DR. CONTI: Today I would propose maybe the term translational trials or some qualifier that would make it a little more clear as to what the intention is, as opposed to the ambiguity that we currently have.

DR. MILLS: Absolutely. Again, remember

one of the other evolutions that we do within the agency is that a lot of the time when we are doing free-thinking with you in terms of guidance development, that is really setting the stage as we go forward in terms of doing our thinking for developing regulations because we know that the regulations tend to get locked down maybe for as long as 29 years. Okay? But we can evolve our guidance much more quickly.

DR. CONTI: Thank you.

DR. SWANSON: Dennis Swanson, University of Pittsburgh. Let me comment on minimal risk. As director of the IRB office I have been involved in this issue. If you are concerned about how they are going to define minimal risk as it relates to children and the children's guidelines, you really need to be addressing your concerns to the Secretary's Advisory Committee on Human Research Protections.

A little bit of background on that, why they are recommending an absolute risk standard where minimal risk is defined as the risk to the

general healthy population comes back to the Belmont Report and the basic principle of justice. Okay? Justice states that the potential risk and benefit of human subject research must be spread evenly across all subject populations. If you have a relative risk standard where you are willing to accept a higher level of risk for people with a disease or a condition, that is a violation of the justice principle. Okay? And, that is exactly where they are coming from in using the absolute risk standard.

What you really have to be concerned about is, you know, the category of pediatric research where the most likelihood of getting our PET studies approved is 50.53 where clinical investigations involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Even under that category, it states that the IRB must find and document that the risk represents only a minor increase over minimal risk.

So, what we really need to be doing as a PET community is lobbying that, as they define examples of "minor increase over minimal risk" that they do so based upon a radiation dose and ED level and not automatically exclude ionizing radiation procedures. Okay?

A comment about quality standards, maybe I am confused but for PET drugs, it seems to me, that Congress has already mandated that all PET radioactive drugs using teaching, research and clinical care must today be in compliance with USP chapter 823 and USP monographs if they are in existence. So, I don't understand today why there is even a question out there as to being compliant with USP standards. FDAMA clearly states under Section 121 that you shall be in compliance with USP Chapter 823.

DR. MILLS: Eldon, do you want to comment in terms of the general concept that you were discussing about the PET issue in terms of the quality issue of that drug, and in terms of the USP standard?

DR. LEUTZINGER: I agree with you that FDAMA mandates that all PET products would comply with USP 823. I mean, we know that; we know that is true. Our only concern has been I guess that, you know, RDRC--it is their responsibility to make sure that all these things--you know, that any PET product that they produce would meet those kind of standards. Our concern is that--well, we are just asking the question how would RDRC manage this; how would they write their protocols so that, in fact, that did occur across all the RDRCs.

DR. MILLS: And in the particular instance that we are describing, it was my understanding they were not in compliance--

DR. LEUTZINGER: Yes, that is true. They were not.

DR. MILLS: I want you to focus on that, they were not in compliance.

DR. LEUTZINGER: Those particular RDRCs were not holding up their end of the responsibility for meeting those standards.

DR. MILLS: Dr. Suleiman?

DR. SULEIMAN: The question of quality assurance or quality control, I mean one of the speakers said they saw inconsistency among the RDRCs. All right? And, complying with one sentence--we have a pretty nicely worded single sentence in the regs but how do you enforce that or, you know, how do you spell it out? You don't want to get too prescriptive but, at the same time, how do you specify enough so that the RDRC committees fulfill their responsibility by the laboratories or the investigators in terms of complying with the regs? If you don't spell it out enough people get away with things or start to get sloppy. If you spell it out too much, then people say we are being overly controlling. So, that is what we are asking.

DR. SWANSON: Well, I consider the congressional act by Congress would probably spell it out enough for me and I would pay attention to it but maybe RDRCs don't do that. Let me tell you that as an RDRC chair, and I know other people feel this way in this room, the unevenness between RDRCs

and the regulation of RDRCs creates big problems for me. You know? I have our PET facility comply with USP 823. We don't allow a first-in-human study by adding a fluorine to a compound. Okay? Other centers do do that, and then the chemists from my facility come and express concerns to me that I am over-interpreting the regs and, you know, I am making it more difficult for them. So, I am concerned, and I think there are probably others in this room, that all PET centers are compliant with the appropriate set of regulations.

DR. MILLS: And I think that that is one of the focuses, in terms of doing this discussion, to reflect that you have various levels of RDRC activity going across your various centers because, in fact, that responsibility and authority sits our there with the RDRC and the IRB to interpret those regulations and to implement those regulations. I can tell you that in some of my discussions with the Society of Nuclear Medicine meeting, up in Philadelphia, there was some variability, if you want to say it, amongst various institutions.

Frankly, every now and then somebody would come up and say, hey, you know what they are doing over there? It is out there, the RDRC and it is out there, the IRB, and you have seen the reg and we anticipate coming forth with some guidance to help in looking at that.

The focus and the development of today's meeting and opening up the docket for as long as we can get it open is to help everyone focus your attention and thought process and, if anything, I can do for you it is to hold up the mirror and let you see from time to time. Indeed, some are very strict; some are very liberal. Frankly, in trying to get everybody under the same tent is the hope and the purpose of where we are going right now.

There was a comment that you had about the IRB and I think that is very, very relevant. My concern is defining what is above minimal risk and how to understand that because, frankly, having been in the oncology area for ten years before I came over to medical imaging per se, even though I was doing imaging over there, it is going to be

very difficult, unless you have the understanding and the interpretation, to eve do an MTD, maximum tolerated dose study, in oncology for pediatrics, unless you understand what that risk is and how you associated and how the IRBs can be comfortable with it.

So, remember, within this room we tend to get a little bit closed in because we are not supposed to have any adverse events but we do. But, remember, you are part of the whole community and what you are going to establish for the IRBs--not just for the RDRCs now; for the IRBs--overlooking these types of studies whether they are in adults or pediatrics, what are those acceptable risk? Frankly speaking, let me tell you in oncology we have an acceptable risk horizon which is vastly greater than what we have for the imaging, and we have to respect that and not affect that area where we need a lot of work and a lot of development. We have to go forward in that area to be able to improve medical care, and part of that is that your tent has to be folded in under there.

More comments? Please.

DR. SMITH: Gary Smith, University of Tennessee. I would echo Dennis' comments with respect to risk and the Belmont Report. That is exactly what I believe Dr. Goldkind mentioned earlier. I don't necessarily agree with it. I agree with Peter that we need to be assessing relative risk in these studies. I think that is what patients want and perhaps there is a way to balance that, and I will leave that to the group.

Secondly, with respect to pediatric studies and federally funded research, currently my understanding is, and I could use some education here, that all studies now require that children be included in research protocols unless there be a specific reason to exclude them from the protocol, such as that the disease does not occur in children or other reason to specifically exclude children from the protocol. But that reason does not specifically mention risk to the child and, therefore, if all studies must include pediatrics and the position of the FDA is that pediatric

studies should all fall under IND, then the RDRC would have no business with pediatric studies, if I am following that logic correctly. And, I think if RDRC is going to oversee pediatric studies we need to resolve that Catch-22. I guess I would ask for comments on that.

DR. MILLS: Dr. Loewke, we had a pediatric advisory committee back in February. Will you give us at least some thoughts in terms of that? We weren't really thinking in terms of discussing that but Dr. Loewke was involved in terms of that advisory committee.

DR. LOEWKE: Yes, but unfortunately I don't have the expertise to know PREA inside and out. That is the new regulation that requires that pediatrics be studied. There is still the option for, I believe, deferral and waiver depending on whether or not the disease exists in children or the relative relationship of the drug for use in pediatrics. But I really would have to defer to our pediatric colleagues on giving you the specifics about PREA.

DR. MILLS: It is an area that is in development. In terms of your comment, it is being strongly encouraged. We are trying to develop it, but--not to use a pun--it is in its infancy as we are trying to get it going. So, we are in the process right now in terms of doing further development and actually involving radiolabeled compounds for diagnostics. So, we would anticipate that we are in the process right now but recognize that not every study is being required. They have means to defer and to set aside that pediatric indication depending on whether it is actually or not occurring in the pediatric population and whether or not we can actually develop enough subjects to be enrolled. But I expect that you are going to see much more activity in that are because of PREA.

DR. SMITH: My final comment has to do with respect to the first-in-human studies. I think that by requiring that non-radiolabeled drug dose toxicity studies be performed in a different patient population we are simply transferring risk

of toxicity of studies from the RDRC to a different set of patients who may or may not benefit, and most likely will not benefit from dose escalation trials to look for pharmacologic effect. So, what we are doing is trading a surely known non-pharmacologic response, as Dr. Taylor mentioned in his discussion and others have mentioned as well--clearly very low risk for pharmacologic response for most of these RDRC protocols, and by requiring those escalation trials to be performed we are putting a larger population, albeit a different population, at significant risk.

DR. MILLS: The understanding in terms of our development there is that with imaging processes and practices we have in place right now we wouldn't necessarily drive an MTD study to just demonstrate a pharmacologic effect for you in the human population. So, from that standpoint, indeed, if you had an experience that showed that there was no pharmacologic effect, that is what we are trying to establish, that there is a human experience prior to moving under RDRC.

DR. SMITH: Either way, that human experience simply transfers the risk to a different patient population. The only argument that I can see that might supersede that is the fact that, by transferring that to a different mechanism, the IND or other protocol, the FDA have that oversight as opposed to the RDRC and the IRB.

DR. MILLS: Right, with the regulation presently that would be the intent and the structure, that someone has had the oversight in a more directly regulatory stance to have that first-in-human experience prior to it going to an RDRC. That is an area that certainly you can comment on in terms of giving us input in terms or that.

DR. SMITH: Thank you.

DR. MILLS: Orhan?

DR. SULEIMAN: I have a question that has been screaming at me, the lack of pediatric studies under RDRC, you can't just ignore that. So, my question is why aren't RDRCs doing pediatric studies? Are the IRBs actually saying we are

interpreting Subpart D and we are not allowing this? I have had one RDRC chair tell me we don't do pediatric studies and I am wondering is that the exception, the rule. I am just curious.

DR. SMITH: I think that has been because of the risk issue. Historically we have tried to avoid pediatric studies because of radiation risk issues, and so forth. But in the future, under the new regulations, we are going to be required to review those or make all of these studies direct IND studies.

DR. CONTI: Here is a radical thought. Those of you who know me know that I come up with these every once in a while. What about requiring, before entering an IND for a diagnostic imaging agent, an RDRC study? Think about that. Require an RDRC study before you can even apply for an IND. The same issue is going to come up in drug development. Drug companies want to use this mechanism, this tool, to look at pharmacology initial studies in first-in-human use so that they can decide on whether a drug should continue down

the pipeline. They should be allowed to do those studies under an RDRC-like mechanism to move the field forward fast. We should have the same opportunity to do that in translational research. This is a golden opportunity to actually change what we are doing, our approach to translational research and drug development. Let's really think about that.

DR. MILLS: Peter, one of the elements in terms of the discussion and part of what we are looking at is, again, I talked to you before about the border between the exploratory IND and RDRC, and in your comments that you are going to provide to us tell us where you see the interrelationship, the overlap and how best that would proceed. Certainly, both of those areas because the commitment for the Critical Path is, indeed, to accelerate drug development and effectiveness in terms of being able to select that portfolio as best you can. And, if early exploratory developmental studies--I didn't say under which mechanism--could be looked at in terms of

developing the evaluation of PK, biodistribution and dosimetry could be performed in an effective and rapid manner, then under which tent would it exist, and why would it be there depending on the community that it is serving and how it is going to be approached. So, as part of what we would be looking for in that comment is to understand how you would see it and what effective tool. The RDRC sits here, within this room but, remember, there is a lot of drug development out there that doesn't handle RDRC routinely so they see the IND as their mechanism. So, when you are thinking about that realize that we are a small group as compared to a larger group and how can we be effective for you, the community, to enable you to do this drug development in the best way possible.

DR. GELOVANI: To continue, the key element is--yet again, I don't want to sound like a renegade here in terms of trying to pound on the issue of the differences in physiologic, pharmacologic and, most importantly, pharmacokinetic properties of what we, at least I

representing all groups of my direct and indirect mentors in this audience, believe. Taking a drug and putting a label on it doesn't make an imaging tracer. Therefore, all the clinical trials that are in the reg, referred to as RDRC, shouldn't conduct the studies which are sort of a clinical trial for evaluation of safety and efficacy of the drug--that doesn't spell diagnostic agents--is the interpretation of this agency to lump everything together.

But then when you start talking about separating, what constitutes clinical trial? What does not constitute clinical trial? You raised the question. What clinical trial? What is the aim of the clinical trial? To better define the question.

If we are talking about that a company or an academic institution developed a drug targeting a certain target, and they would like to study biodistribution or kinetics of the drug to address the drug pharmacology and maybe then put a radiolabel on such as rhenium on it in the chelate variant, or there is an antibody that they try to

develop and if it doesn't work therapeutically without the label we put a label on it ala zevolin, conducting those clinical trials to assess efficacy but not biodistribution. The efficacy under RDRC will actually be in conflict with the regulation.

But let me ask you this, if we are developing a new imaging agent that is targeting a specific biochemical process or physiologic process, because in fact in '72 there wasn't such a thing as molecular biology or genetics so let's add to it molecular biological process, i.e., signaling kinase activity--I am not even developing a diagnostic test. I am not going to be diagnosing tumors with that. I will be diagnosing or sub-profiling those tumors with respect to their signaling activity which then might be interesting for a selection of a new drug. But that doesn't constitute a clinical trial from what the regulation was talking about.

In principle, Peter is right. All of these are clinical trials but in relation to the regulation this does not constitute a clinical

trial. Using FLT which will be imaging the DNA syntactic pathway activity or at least reflecting it in the context of a variation of a new drug does not constitute clinical trial to evaluate FLT. It is a clinical trial to evaluate the drug. And, if the drug is approved but we are simply trying to select which patients are responding and which are not under the local IRB provisions and we would like to evaluate is the new cytostatic agent really inducing the change in DNA proliferation, by what is reflected in the regulation we are studying the chemical process or microbiological process using tracer FLT. That should not go under the provisions of IND, if I interpret that correctly.

I can bring you so many different examples of that. If we just fail to recognize the difference and lump everything together in the reg, we will kill a lot of interest in the science, a lot of interest in developments which ultimately the population with cancer, and I speak for cancer not for anything else, will greatly benefit. That is the key.

What I believe, and I echo what Peter said, is that without knowledge what this accelerated or simplified IND mechanism is about we cannot make our judgement. However, correct me if I am wrong, the IND doesn't spell out specifically diagnostic radiolabeled agents. Again, if I may boldly summarize or fantasize about, it lumps the drugs, the radiotherapeutics and maybe diagnostic radiolabeled agents, all together. Please don't do that. These don't belong together. Even a biological radiolabeled beta emmiter or gamma emmiter to induce radiotherapeutic effect should be segregated from the diagnostic agent.

And, all this discussion about, oh, it is a matter of dose only is valid but, up front, if we just say the intended use of that would be diagnostic as opposed to therapeutic. If you take FDG and give a curie and announce to the patient, yes, it will kill the tumor but you will kill the brain as well--so, we need to remember about those things when developing regulations because you regulate; we follow but we cannot follow on a path

which leads nowhere.

DR. MILLS: I think one of the elements of that is why regulations take a long time in their development. Jerry, did you want to make any comments related to that? Then I have some follow-up comments.

DR. COLLINS: Essentially we will interpret your comment as a suggestion to us on how to proceed in the revision. Philosophically we may agree or disagree. We interpreted the current regulations as best we can with the help of an incredible pile of government lawyers who oversee the effort, and we are stuck in that box. We inherited all this language. I don't think any of us actually worked for the FDA in 1975 so we have inherited this language. We have to live with it. We have to live with the fact that regulation begins by calling these things generally recognized as safe and effective. That is an extraordinary term to use for something at this stage of its life cycle. So, we are going to be stuck with some disconnects between what is a clinical trial; what

is not a clinical trial; what is a drug; what is a diagnostic. There are parts of the regulations where something that everybody is a diagnostic is defined by the Food, Drug and Cosmetic Act as a drug. We have to live with this.

The important thing is to find out what kinds of studies you feel are being inhibited. As you stated in the middle of your remarks, what is inhibiting innovation; what is killing science. That is what we have to zero in and focus on. Whether it is a regulation change or a guidance change, your suggestions on how to prevent the decline of innovation is what is really important to us.

DR. GELOVANI: As well as cost and as well as common sense.

DR. COLLINS: I don't think you break out cost separately. You can just assume that if you don't have innovative new products there is going to be a large cost associated. Our agency doesn't deal specifically with dollars. We are much more impressed by unmet medical needs, by lack of

innovation. Our mandate, except in the context of generic drugs, is not particularly related to the cost.

DR. GELOVANI: Agreed. Why then not separate into radiotherapeutics, radiolabeled drugs for PK/PD, and truly diagnostic agents?

DR. MILLS: Let me focus for you for just a moment. Peter had his radical idea just a moment ago--

DR. GELOVANI: It is not so radical.

DR. MILLS: Well, that is why I want to focus for you because a part of what we will be dealing with is starting to define and we are going to need a lot of input from the various societies and various organizations to also give us this focus because I am concerned that, as we wordsmith--most of the people in this room, when they say diagnostic they think of an image. You remember from my slide, they have a whole subset under RDRC that is non-imaging diagnostics. Also, I have been hearing today about doing Phase I and Phase II development under RDRC, but then I am

hearing that radical idea over here, that sounds also pretty good, what if we require what basically sounds to me like a very basic PK biodistribution study and propose that that is where RDRC should be.

DR. GELOVANI: Absolutely.

DR. MILLS: So, suddenly I have a spectrum that I was trying to describe and, again, the word challenge becomes immense. It is just like we were talking about the patient populations. Be sure and define that for us. Also be sure and define what you are seeing in terms of that spectrum because, frankly, everybody here--we all tend to get into our own cottage and the only thing they are going to do under RDRC is PET. Okay? The only thing we are going to be doing under RDRC is diagnostics, or it is going to be the non-imaging basic research. You have to be able to get it all underneath that structure, and how far and how aggressive do you want to be?

If you go to a limited model and say let's hold RDRC to PK and early development but make it

be the front end. That is a concept. You could really put it in a key position. That is a potential. Or, we wanted to expand in doing Phase I/II development. That is a much broader extent. Then we have to think about the exploratory IND and how well that would facilitate for you the same way.

So, these are all of the elements and we need your input to tell us that spectrum of what we should be thinking about. That is why we are probably going to go to guidance and then start working on a reg as we start to refine those thoughts because, frankly speaking, it did real well in 1975 but we have kind of gotten the science and the medical development beyond that thought process and that is really what we have to flesh out right now. That is why this is so interesting because this wordsmithing that we are getting into is the essential pieces if we put this together in 2007 or 2008 and somebody in 2030 is going to look at it and say, oh, my gosh, what was George thinking about? Okay. And, George was trying to

think with the community and trying to think with the people around him and say, no, we have to all get the input in. It is a collective idea.

DR. GELOVANI: I guess we all welcome this. This forum really is a fantastic opportunity to exchange these opinions. But just a last comment, I don't think, if I understand correctly, that Peter was trying to limit the focus of the RDRC to just the PK/PD--

DR. MILLS: I didn't infer that. I just wanted to focus you because we are dealing with such a wide spectrum of input now, and what I want you to do is to try and each time, as you write your comments, think about all of the other pieces and parts we are going to be dealing with. As you were saying, we don't want to close out a whole element because we focused on one element alone.

DR. GELOVANI: Thank you.

DR. MILLS: Other comments?

PARTICIPANT: I just want to try to answer Dr. Suleiman's question about why aren't there more pediatric studies. I think that in many places the

IRBs take the view that any radiation is a very big risk. So, that is the first thing. So, there are many institutions in which PET studies or SPECT studies just really can't be done. Even in places like at our institution where they can view it in different ways, many times they will feel that the risk needs to be balanced by some potential clinical benefit to the patient. Then, since the RDRC doesn't really allow that, the RDRC is sort of excluded from being the mechanism by which you could do that study.

I feel very strongly--I am a pharmacologist and I am in the division of clinical pharmacology in a children's hospital and I also part of a pediatric pharmacology research unit, and we are sort of grappling with regular drugs with all of these same issues. The way the drugs are used in children is really adapted from these adult studies without any studies in children, and we know that their physiology is different. And, we really need to step back from saying that for ethical reasons we can't do this. For ethical

reasons we need to figure out some ways that we can do this. I think that as we think about this we need to define what is an acceptable level. Maybe it is not completely safe, but if we are going to exclude a whole segment of our population from this technology we better have a pretty good reason for it, not just some theoretical risk to children. That is all I have to say.

DR. GARNER: Colin Garner, from Xceleron. I would just like to follow-up on the pediatric issue because we have talking about microdosing in relating to thinking about drug development, and I think we are focusing on human volunteers primarily but, of course, microdosing would be a way of getting a handle on studying the metabolism of drugs in children and in infants because there you are administering literally a sub-pharmacological dose and the quantities of radioactive can be very small. The smallest study we have ever done was with 100 Bq in an adult. So, we are talking about very, very small doses of radiation exposure here.

This is a situation where you can do a

microdose study in an adult and get some information about the clearance of your drug under those circumstances, and then do a similar type of study in an infant or in a child and see whether the drug is cleared at a similar rate as the adult or not. On that basis you would determine what likely doses you should be administering.

So, there are lots of ramifications actually of these trace doses, and I don't want you to think that they are only specific for looking at, say, candidate selection.

DR. MILLS: Other comments?

[No response]

We have a Federal Register notice and this room has to stay open until 4:30 and the microphone has to stay open. I am going to stay here. Okay? So, all of you in the room understand who has the responsibility. Okay? And that microphone is going to be open. If anyone wants to come to the microphone, I am going to stand right here with it. Otherwise, if you are disappearing, it has been a sensational amount of input and I really appreciate

it and, remember, we have another 60 days, at least 60.

[Whereupon, at 3:40 p.m., the proceedings were adjourned.]

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