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UNITED STATES

NUCLEAR REGULATORY COMMISSION

ADVISORY COMMITTEE ON

THE MEDICAL USES OF ISOTOPES

Hyatt Regency - Crystal City

Jefferson/Kennedy Room

Friday, May 10, 1991

8:30 a.m.

PROCEEDINGS

[8:35 a.m.]

DR. SIEGEL: Good morning. We have a go, so we need to resume where we left off yesterday. Our single item of business for today is discussion of the interim final rule and then discussion of the remaining issues associated with the ACNP/SNM petition regarding radiopharmaceuticals and their preparation. We dealt, as you know, with the quality assurance rule last evening. Dr. Morris, from the Office of Research, is here today, and he and I have had a chance, prior to the meeting, to discuss whether there would be any additional need for him to make the presentation that he would have made if we were going to do it this morning, as per the original schedule, but we mutually agree that yesterday's discussion handled all the information that needed to be addressed by the committee.

With that, let us move on to a discussion of the interim final rule. John?

[Slide.]

DR. GLENN: We rearranged the set-up last night, hoping to make it a little easier for the committee members to see both the screens and the audience. I realize now that there is a post and that some people may not be able to see at all, so I'll give people a little chance to move around, so that you can see the slides as they're presented.

The majority of this discussion this morning is going to be on the remaining issues of the petition. This tends to be a status report on the interim final rule.

I'll jump down to the third bullet here, that says "The Syncor Petition," because that's going to have a major effect on what I am able to say and comment on this morning. I think most of you are aware that last September Syncor did petition us to withdraw all or portions of the interim final rule and that in October they filed a suit in federal court on the same issue. Since October, the Commission and Syncor have been in negotiations to see whether this can be settled. We are helpful that resolution is coming soon; however, we are not at liberty to discuss what the negotiating issues are, what the positions might be, and the outcome. I realize that's frustrating to everyone, but that is the situation we're in, so many of the things you would like to know most I'm not going to be at liberty to discuss.

What I will talk about is status and interpretation of what's already out there, but in terms of what happens next, unfortunately, I'm going to have to be a little circumspect.

The first bullet is to talk about data collection. In terms of actual data collection by the NRC, there has been none at this point. I'll explain that a little bit, in that the guidance that we wish to send out to the regions

could be affected by the negotiations in the suit, so we have been holding up until we know the final resolution there. We have thought of other methods to get the data, and so forth and so on. That is not resolved at this point.

We have received communications and information from medical groups, Society of Nuclear Medicine, ACNP, ACMUI members. I think we feel we're beginning to get a fairly good picture of what's actually going on out there; however, we're not in a position at this point to analyze the data, let you know conclusions, or come to you for advice, based on the data that we have. I wish we were at that point, and we hope to get into that mode as soon as we can.

We did provide a response to the ACNP and SNM in a letter dated January 9, 1991. That was our attempt to clarify the issues surrounding the interim final rule, and this morning I'm going to try to give some highlights and see if I can do any better. Obviously, I'm not going to change the wording in the letter, because that was carefully drafted, and so forth and so on, but maybe I can point out some highlights, a little bit of the history of how we got into the interim final rule.

One thing that it notes is that the interim final rule was intended to permit departures that were physician-driven and in the best interest of the patient. I

think that was certainly within the Commission our sense of what the petitioners were asking for. The words we chose to describe that were "to obtain medical results not otherwise obtainable by strict adherence to the package insert" or "to obtain medical results not otherwise obtainable." The rule requiring that a statement be made, defining why the procedure, the change, the departure, meets one of those two criteria, was based on our eagerness to be responsive, to not delay taking action, so that what we came to conclude were necessary procedures would not be impeded.

To have an immediately effective rule, you have to have justification, and our justification was that indeed these procedures were necessary to obtain medical results not otherwise obtainable and to reduce risk to a particular patient. I realize, by making that a record-keeping requirement and a requirement that there be a written directive defining that, that the medical community feels we imposed an unacceptable burden, but that was certainly the thinking behind it.

The rule did require that it be documented, and there were three elements that had to be there: the nature of the departure, and then the reasons, as we've just discussed, why it's in the best interest of the patient. We tried in the letter of January 9 to clarify that we were not in any way using this documentation process to try to

second-guess medical decisions. We wanted the information so we could evaluate what the effect of the interim final rule itself was, what procedures were actually done, what were the reasons for them being done, so forth and so on. This would be the basis, then, for us making a decision as to whether future rulemaking should involve extending the interim final rule, doing away with the requirement to file the package insert altogether, or going back to what we had before the interim final rule, which would be a more rigid adherence to the package insert. So the information, the recording, was intended to be a way for us, at the end of the three-year period, to be able to come to a conclusion about what was the next step in the rulemaking.

Now, there has been a lot of sensitivity to the enforcement issues, what is the intent of the NRC, what would the NRC enforce with regard to this rule. Clearly, since there is a record-keeping requirement, failure to make a record that has the information there would be a violation of the rule as it has been printed. The letter goes on to say that failure to do that would be a severity-level 5 violation; in other words, it's a failure to keep some information that the Commission wanted. Normally that kind of item is our lowest level of concern in terms of violation.

There is a statement that, if willfulness is

involved, or if the violation is indicative of a breakdown in management control, then more severe sanctions might be there. That was not meant to be a draconian statement, but simply that our enforcement policy requires us, where there is evidence of malfeasance and deliberate, to consider that in terms of our enforcement and react appropriately, so there cannot be a blanket denial that we might take strong enforcement, because we can't anticipate all the situations that might arise. I can't come up with an example where I think this would actually occur; the best I can do is think of an analogy that, if my neighbor wanted to park his car in my driveway and he said he had good reason for doing it, I'd probably say, Go ahead and do it; but if he asked me to put in writing that, no matter what happened, I didn't have any concern about that, then I might, you know, have some second thoughts about it and want to put in some provisos: provided that you don't make a public nuisance, you don't break the laws, this kind of thing. That was the intend of the statement there, that if there's not a deliberate, willful attempt to get around the regulations -- we have to keep open the option of strong enforcement if that occurs. I personally can't imagine a motivation for someone here or in the medical community to do that, but I think in terms of the letter we can't deny that things could happen that might lead to strong enforcement.

The final thing that the letter pointed out was that, for many of the departures that we were getting phone calls about at the time, in fact we had given relief to that previously. There was some concern about routes of administration and indications of use for diagnostic procedures. The letter does go on to point out that in fact we had dropped those restrictions in previous revisions and that there is no reason under the interim final rule to document diagnostic departures from the package insert with regard to routes of administration and indications of use.

Those for therapy were new and were included in the interim final rule.

Finally, we tried to clarify a little bit about the status of broad-scope licensees. Basically, for a broad-scope licensee that permits medical diagnosis, medical therapy, or medical research with radioisotopes in any form, the interim final rule is not applicable, and in fact the record-keeping requirements are not required. It's interesting because we did get some communications from a survey that was done among broad-scopes indicating the types of departures that were being made and the frequency, at least among institutions, of these departures being made. I don't know whether someone in the audience will want to talk to that today or not, but we have received that information. My expectation is that, if this information is available, we

will be quite willing to collect it and look at it, but it will not be a requirement that those records be kept and that that information be made available to the NRC.

Those are the highlights of the letter that was sent out January 9. We had hoped that it would resolve and make some of these things clearer. The feedback that I've gotten is that that is not the perception, that we have cleared up all these issues, but that was certainly our hope. Maybe some of the things I've said today clarified things a bit.

Finally, we did receive another letter, dated April 8, co-signed by the ACNP and SNM, that essentially asked us to withdraw the interim final rule. We are responding to that. The response to pre-decisional, and so I can't really go much beyond that and tell you what we're going to say.

So that's the status.

DR. SIEGEL: John, just as a point of clarification, at the January meeting, in talking about the content of the January 9 letter, one of the issues that came up -- and it's probably just worth clarifying again for the record -- was that your intent does allow for the possibility of certain types of generic deviations --

DR. GLENN: Oh, yes.

DR. SIEGEL: -- whereby a deviation is built into

a department's procedure for a particular type of examination based on the physician's written directive that underlay that procedure that this deviation is necessary in order to perform the procedure in a particular way.

DR. GLENN: Yes. There were essentially three ways that the written directive could be used. One is for a particular patient. That would be the most onerous in terms of record-keeping, where every time there was a patient and there was a departure in the preparation, you had to state the reasons and keep the records and maintain the record for that particular patient. But the rule provides also for a type of procedure or for a radiopharmaceutical. If within your institution the authorized users decide that you want a departure to be used every time you perform a certain procedure or prepare a certain radiopharmaceutical, you merely need one record, and then you do need to track how many times you act upon that, but that means basically that you need to know how many times you do that procedure and have on record one statement of why you're doing it that way.

We did try to design it so that we minimized the paper impact.

DR. SIEGEL: I thought that was just an important point to clarify one more time, so that people do understand that that was allowed in accordance with the original

language in the interim rule.

DR. GLENN: Yes, and it was our expectation that that's the way that it would be done.

DR. SIEGEL: Questions? Dr. Goodrich?

DR. GOODRICH: Based on personal experience with an inspector, I would ask that, in the unhappy event that this does remain in place and in the protocol I have a departure as you all perceive it, is it in the realm of license of an inspector, on the basis of my procedure, which constitutes a routine departure in your terms -- is it in his purview to require me to pull all of the patient records for a period of time or to cite me for failing to keep a list that's separate and apart to document those multiple departures under a procedural protocol?

DR. GLENN: In terms of what records the inspector can look at during the inspection, I guess that would depend upon the items that he's looking at. Now, in terms of this rule, it was not our intent that you keep an extensive file on each departure, patient, and this sort of thing. Now, routinely our inspectors do look through the administration's notebook that's kept normally in the hot lab, and so forth and so on. They do look for unusual things, and so I think that would continue to go on.

At this point we have not -- we have essentially told the inspectors not to be inspecting this item and that

the guidance will be coming out, so the final guidance has not been sent out, and that would be pre-decisional. But it is not our intent to do anything other than gather the information about what types of departures are made and how frequently they are being made.

DR. SIEGEL: Dr. Marcus?

Carol, I think you're probably going to have to go into the audience and speak from that microphone, and you're probably going to have to do that for most of the things we talk about today.

DR. MARCUS: Okay.

DR. SIEGEL: Let the record simply reflect that, because Dr. Marcus is identified as an important contributor to the original petition on behalf of the SNM and ACNP, procedural rules require that she address the advisory committee as a member of the public rather than as a member of the committee, and she will not be allowed to vote on any motions that might pertain to this item or the remaining issues of the petition.

DR. MARCUS: Okay. Thank you very much.

DR. SIEGEL: I can't imagine why you'd thank me for that.

DR. MARCUS: I'm trying to be a lady.

DR. SIEGEL: Yes, dear.

[Laughter.]

DR. MARCUS: First of all, I think it's important to realize that many of us object to the title, the remaining issues of the petition. I think all the issues are remaining. I don't think anything has been solved at all. I appreciate the fact -- and I think most of us do -- that NRC did try to address one of the more onerous and immediate problems we had that led to the petition. There were many problems involved in the way the final wording came out in the interim rule, and it is not your efforts to help us that we are trying to put down; it was some pretty funny last-minute wording that just simply was not what we considered to be in the best interests of the efficient practice of medicine.

Before I go into some material that has been distributed about the interim rule, I'm going to do what I did yesterday and tell you how California decided to handle this whole thing. First, they wanted to know what the legal status of the package insert from the FDA was. They had been told by an individual at NRC that it was a legal requirement and that it was against the law to deviate from a package insert. I said, No, that's not true, and brought them about half a dozen articles published by the FDA in the open literature describing the package insert as an informational document. I then brought them a letter from the FDA to Syncor telling Syncor that they were not

obligated to follow the package insert but that, if they departed, the FDA was not responsible for the qualify of the drug that was produced, but that, since the pharmacy was willing to take that responsibility, that was perfectly within their rights as professional pharmacists.

These letters were sent to Dr. Tse in the fall of 1989 -- no, '88, after the petition was submitted -- sorry, '89. It was also sent to Dr. Howe, Mr. McElroy, Mr. Cunningham. I have this litany of names I send everything to, just in case people don't talk to each other. So all those letters were received. The letter to Syncor from FDA was re-sent out, in case anybody didn't read their mail, a short time ago.

[Laughter.]

DR. MARCUS: These letters were also brought to Sacramento.

I'm just going to read you three new license conditions that Syncor has in California to demonstrate to you the difference between your rather complex way of looking at this and how 20 percent of nuclear medicine in this country looks at this. Condition 20: "Except as otherwise specifically provided by this license --" -- basically -- "-- radioactive pharmaceuticals to be administered to humans shall be procured in prepackaged, precalibrated form from a supplier registered with the FDA

in accordance with the Food, Drug, and Cosmetic Act, or prepared and compounded from a prescription in accordance with the regulations of the California Board of Pharmacy." Same thing for biologicals. Same thing for cold kits.

Basically, the rad health people in California made the following statement: We are not drug regulators; we need one. We don't care if it's the FDA or the board of pharmacy, but one of you guys is going to take responsibility for drugs. So what they are basically saying is, As long as we don't have to judge drug quality, you make them according to the board of pharmacy or, if you're a manufacturer, you make them according to the FDA.

Syncor has no obligations to do anything but practice the best-quality nuclear pharmacy they can. Any physician in California can write a prescription; they fill it. That's a lot simpler.

Basically, de facto, that's what's been going on anyway. There have been license conditions over the years, but no one has really paid much attention to them, because the deputy attorney general of California, Bill Marcus -- no relation except in spirit -- who advises the board of pharmacy, basically stood up and said, If anyone in this state makes a regulation or a license condition that tells a pharmacist he cannot practice his profession according to the state law, he can see me in court. It was perfectly

understandable to the rad health people what that meant.

So things are very simple and clean in California. I suggest to you that you're not going to find a lot of radioactive bodies out on the West Coast, but I'm sure your region V people will be counting them up as they occur.

The NRC requested at the advisory meeting last January additional information about the interim rule. I had presented a rather thick document for your consideration in November that put together every departure from package insert that I and my more learned friends in the nuclear pharmacy field could think of, and tried to estimate the approximate number of such deviations -- or departures -- were we free to do them, also pointing out that most of the more innovative ones were practiced in broad-license institutions and these were just the people who would not be reporting to you; therefore, you would never know about that, and you might be lured into the erroneous thought that nobody needed to depart from package inserts, where in fact that was not the case.

Dr. Naomi Alazraki, who is here with us today, requested that Dr. Ted Silberstein, the chairman of the pharmacopeia committee, do a study -- or expand a study that was already going on tracking adverse reactions to radiopharmaceuticals, so see whether any of the adverse reactions were related to departures from package inserts.

The report of the pharmacopeia committee has been distributed to the membership of the advisory committee and to the NRC. I think it went out probably about a week ago, or something like that, rather short.

Dr. Silberstein had been collaborating with 20 nuclear medicine departments, virtually all of which were broad licensees, and the adverse reactions were collected after the administration of about 221,000 drug doses. As you can imagine, the number of adverse reactions is very, very small. There are a few idiosyncratic reactions, mostly to MDP kits. What he determined was that none of these adverse reactions had anything whatsoever to do with package insert departures; that in fact these institutions were averaging, sort of generically, at least three major departures apiece; that they were necessary for the good practice, or the optimal practice, of nuclear medicine and nuclear pharmacy' and that, in the opinion of the pharmacopeia committee, the NRC should not worry that departures were detracting from quality but, rather, improving it.

It's pretty hard, as I think NRC understands, to gather huge amounts of detailed data. I think that the information, though, that Dr. Silberstein collected should be very useful in the deliberations of the committee.

Later on, when the chairman is ready, I guess I'll

get into the other parts of the petition, but right now I think that's all I have to say.

DR. SIEGEL: Thank you.

The report from Dr. Silberstein that came by way of the Society of Nuclear Medicine, that's a document that you all have.

DR. GLENN: Yes.

DR. SIEGEL: Does this need to be made part of the minutes in any way, or part of the transcript of the meeting?

DR. GLENN: I don't see any problem with doing it, since Carol referred to it.

DR. SIEGEL: No problem?

DR. GOODRICH: In the interest of officialdom, I commend this communication to the NRC with the advice from the committee that they view it as a document of scientific merit, worth of the arguments in regard to eliminating the final interim rule.

DR. SIEGEL: Well, just for the sake of making the information officially available, let's just see to it that this is appended to the transcript as information that was provided at the meeting.

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DR. SIEGEL: Okay. At this juncture, are there other questions for John about his interim rule status

report, or other comments?

Dick, do you want to make a comment?

MR. CUNNINGHAM: If we're ready to talk about the interim report.

DR. SIEGEL: By all means.

MR. CUNNINGHAM: With regard to the interim report, I think it is a helpful document. I, in my quick reading of the thing, made a fundamental error, because you listed 200,000-some procedures, and then you listed the number of adverse reactions, the number of cases. Then I looked at the column of the number of institutions deviating, and the column of numbers there adds up to 76, so I thought, Well, 76 deviations out of 200,000, and it's wrong. What I would like, if we could get it, is the denominator there. We have 200,000 -- or the numerator, rather.

DR. MARCUS: We understood that you would of course want that information. I talked to Dr. Silberstein about the possibility of getting it. He groaned and said, Do you understand how much work that would take? I said, Well, I know they'll probably ask for it. He said, I can't do it; it's an enormous undertaking.

He has given you generic categories of departures. I think there is not enormous disagreement with the estimates that were end in the November report because they

were basically obtained by asking people, including Dr. Silberstein, What would you guess would be the sort of average number, and basically I think, if you took about half a dozen very experienced people in nuclear medicine and nuclear pharmacy and talked about guesstimates, and they were pretty close, and you averaged them, it's probably reasonably accurate.

I still do not understand why NRC would require more detailed data, nor do I understand what it do with those data. I didn't understand that before, and I don't understand it now. I think you have enough information to understand the departures, understand that they are common, understand small, medium, and large -- which is basically, I think, what you really need, if anything, to know -- and make decisions based on that. Unless you can give us some really compelling reasons for the absolute necessity of exact numbers, I don't see why so much work should be undertaken. I think you can make a good judgement without any more.

DR. GOODRICH: Mr. Chairman, it occurs to me that a corollary to Dr. Cunningham's request would be to ask for the similar numbers that apply to the item that was included in this document that NRC distributed, in draft, not for publication, "Quality Management Program and Reportable Events," where they report this vanishingly small number of

misadministration occurrences without the other part of the fraction. If they would like to have the material that Dr. Cunningham asks for, then I think maybe the public needs the other half of their fraction also.

DR. SIEGEL: Captain Briner?

CAPTAIN BRINER: Duke University Medical Center is one of the participating institutions that is present in that report with regard to adverse reactions. Curiously enough, we were never queried about departures by that committee, and I find that hard to understand, why were we discriminated against, because I can think of at least one every Monday through Friday of every work week that we do; we deviate. There you can add a few more numbers to your list. But we were never actually queried about how many of those things we have.

DR. MARCUS: There were a couple of institutions Ted was trying to get a-hold of. Captain Briner, you're such a busy politician, maybe he didn't get you on the phone. He is running two hospitals, too, and running around, and he said he tried. I'm sure he tried to get a-hold of you. There were only a couple that he said he didn't get really good information from.

DR. SIEGEL: Dick?

MR. CUNNINGHAM: Perhaps we're belaboring this point too much, but there is a reason to get the number of

departures -- not a precise number, but some approximate number. It helps the justification of the rule. That's the purpose of it. It does seem to me that, if an institution prepares a radiopharmaceutical for a given procedure in a certain way that's a deviation, they ought to have a rough estimate of how many times they use that. What I'm looking for is some approximation of the frequency of these deviations. It seems to me that you went far along this line, but not quite far enough.

DR. MARCUS: There is a real prob. .. with what you want. It's like the mixed-waste issue: You make a law that says you have to get rid of it within 90 days, but if you do have it there's no place to put it; so, when you ask people, Do you generate any mixed waste, they say, Oh, of course not, because it's illegal to possess it. When Dr. Silberstein was asking some of these participants about departures, the first answer he got was, We never depart from package inserts, especially from NRC licensees. People don't want to admit the enormous numbers of departures they really go through, because they're terrified.

DR. SIEGEL: Carol, I respectfully disagree. The interim rule requires that medical licensees keep track of the number of deviations that are occurring in their laboratories. The board licensees may not have to do it; therefore, the broad licensees were the wrong people to ask

for the information. The point of the discussion at the last meeting, irrespective of whether one believes that having the numbers will aid the decision-making process or not -- I know you do not think that the numbers can change the decision-making at all, and I respect your opinion. On the other hand, the NRC has said they want the numbers, and they've put in place a three-year mechanism to gather the numbers.

Now, there are two ways to play the game. One way is to let the three years play themselves out and see what the NRC does at the end of three years. The alternative that I suggested at the last meeting was to try to provide some information in advance of the expiration of the three-year period so that the NRC could be prodded, by virtue of having data in hand, to make a decision sooner. I am certain that there are licensees whose data base could be tapped and who could provide, for any given six-month period, the actual number, as well as the type, of deviations from package inserts that they have on a day-to-day basis. I know and you know that I'm able to provide those data in about 15 minutes from my nuclear medicine computer. Many licensees cannot, but that does not mean that it would not be possible to obtain an estimate, with some recognitions of the limitations of the sample. That information then, in the hands of the NRC, can be used

as a piece of data.

Right now they don't have any data, other than this number, the denominator of which, by the way, is 20. The answer is that these 20 institutions perform an average of 3.8 deviational practices each, but it doesn't tell you whether they do that 30 times a day or one time a day.

Now, I'm inclined to agree partially with Carol that knowing whether it occurs every 15 minutes or once a year probably doesn't change much from a decision-making point of view. The point is understanding that it's being done when the practice need arises and that there is a rational, medical basis, or a pharmaceutical basis for so doing.

So I'm part siding with the posture that she's taking, but at the same time I'm also suggesting to Carol and to Naomi Alazraki, sitting out in the audience, that, rather than saying we can't get the data, we could be a little bit more creative, or the community could be a little bit more creative about getting the data to you faster than you're going to get it from your own inspectors, since you haven't really started gather it yet from your own inspectors.

MR. CAMPER: Let me add, if I may, to what Dr. Cunningham and Dr. Siegel have said. As Dr. Glenn pointed out, in the staff requirements memorandum that came back

from the Commission as a result of this rule, the staff, which of course I have a great deal of interest and concern about, is charged with, at 20 months into the rule, preparing information and informing the Commission as to what we think we're going to do about the rule once it goes through its three-year sunset provision. At this point in time, as Dr. Glenn pointed out, we have not instructed the regional inspectors as to the gathering of information because of the Syncor petition and possible ramifications associated with that, and do not take any steps that would at all jeopardize or influence those negotiations.

The meter is running. I recognize that a number of this group is opposed to the rule, but the rule does exist in its current form. I can only emphasize that the need for this type of data in a timely manner is extremely beneficial to us from a staff perspective.

DR. GLENN: One thing I would note is that one of the areas that we're really missing the information on is the community hospitals that may not have members of the Society of Nuclear Medicine there, where there are other specialists, diagnostic radiologists, who are running the program. We at this point have very little feel whether there are any departures being done there, many departures. This is an area that we have not gotten any information on at all.

DR. MARCUS: Many of those small licensees that you're concerned with, Dr. Glenn, obtain their radiopharmaceuticals from centralized nuclear pharmacies. The physicians who run those services are really not particularly aware of how the centralized nuclear pharmacy prepares the radiopharmaceuticals. The best people to ask that question to is not the licensee physician but the centralized nuclear pharmacies, I believe. Remember, 54 percent of the drug doses in the United States -- and mainly they take care of the smaller licensees. Dr. Siegel makes his own; I make my own; but we are large institutions.

DR. GLENN: And you realize, of course, you brought up just precisely the issue which we are very sensitive about.

DR. MARCUS: That's right. We have a Catch-22.

DR. ALMOND: Can I just ask a quick question?

DR. SIEGEL: Yes.

DR. ALMOND: Is it true, from reading this report, that none of the adverse reactions that were listed here were associated with the deviations?

DR. MARCUS: Yes.

DR. GLENN: Was there one from the audience?

DR. SIEGEL: I think I was going to handle that in a formal manner in just a moment.

DR. GLENN: Okay.

DR. SIEGEL: Any other questions specifically pertaining to John's presentation from members of the committee?

[No response.]

DR. SIEGEL: I see that Dr. Eric Jones has joined the group. He probably doesn't want me to say this, but Dr. Jones is the group leader for radiopharmaceuticals in the division of radiopharmaceutical surgical and dental products at the FDA. I just want to welcome you.

MR. JONES: Thank you very much.

DR. SIEGEL: Good morning. We're about to enter into discussion of items where we may call on you from the audience to help answer some questions.

MR. JONES: I'd like to make a suggestion. Next year why don't you hold this in Kansas City or somewhere convenient?

[Laughter.]

DR. SIEGEL: We thought we'd have it in Canada for you, Eric.

At this point in the agenda, what I would like to do is recognize, in whichever order they choose, Sharon Surrel and Naomi Alazraki, who had prepared statements that they wish to make before the committee, it was my understanding. Let me point out that, in the process of making your statements -- and I understood you had reason to

comment both on the quality assurance rule and on the issues relating to the petition -- that the quality assurance rule matters were discussed last night by the committee, and we're not going to reopen that discussion in any substantive fashion this morning. If you plan to make comments on that, keep them quite brief, and focus on matters relating to the interim rule and/or the petition.

DR. GOODRICH: Would it be worthwhile for their information to recite the motion that was made by the committee in regard to the quality assurance issue?

DR. SIEGEL: We can do that.

DR. GOODRICH: I believe Dr. Herrera had a comment for you.

DR. SIEGEL: Mr. Cunningham?

MR. CUNNINGHAM: If you're going to do that, Mr. Chairman, I was going to ask close to the break for the committee to confirm something I've written out here on just what that vote was, because we've got to get it into a Commission paper that's going up to the Commission this afternoon, so I wanted to be sure, since the transcript will not be ready, that this is what the committee voted.

DR. SIEGEL: Then let's take that as a matter of business right now.

MR. CUNNINGHAM: Okay.

DR. SIEGEL: Let's even make it clearer. If

you'll tell us your statement, we'll do a roll call vote and make it all part of the official record.

MR. CUNNINGHAM: Okay.

After being briefed on the general content of the QM rule, which incorporates most of the committee's recommendations, the committee voted on whether or not the rule is useful and needed. The majority voted that it is not, with two members voting for the rule and three members abstaining.

DR. SIEGEL: Say that again. Oh, two members voting for the rule and three members abstaining.

MR. CUNNINGHAM: Correct. The majority voted that it is not needed or useful. Two members voted for the rule, and three members abstained.

DR. SIEGEL: And the actual number in the majority was six.

MR. CUNNINGHAM: Okay. I'll put that in.

DR. SIEGEL: And the motion was made by Carol. Was that a reasonable statement of the motion as you made it?

DR. MARCUS: What I meant to convey was a generic recommendation about the existence of any such QA or QM rule: that no matter what it said we recommended that there be none.

DR. SIEGEL: I think those words are consistent

with those words.

DR. MARCUS: I think so.

DR. SIEGEL: They're not so far apart as to disagree with each other.

DR. MARCUS: Except to add that one of my points was, it's not only that it was not needed or useful, but that it was not in your mandate to have such a rule at all.

MR. CUNNINGHAM: In my recollection, that wasn't within the scope of the vote.

DR. SIEGEL: I don't recall that that was in the motion.

MR. CUNNINGHAM: That really goes beyond the -- that's a legal question.

DR. SIEGEL: I would encourage the advisory committee to avoid acting as a grand jury or a federal court and, rather, to provide scientific advice.

DR. HERRERA: Mr. Chairman?

DR. SIEGEL: Yes, sir.

DR. HERRERA: Is it appropriate to state that, for one, I did not quite understand the motion the way it has been presented. That's what I voted against it. So, if I may, I would like to change my vote so that the record contains that I am voting against the rule.

[Discussion off the record.]

DR. SIEGEL: Since this is an important issue,

since this is going to be appended to a Commission paper, I think for the sake of the record we should vote on this again and take a roll call vote.

MR. CUNNINGHAM: Will somebody frame the question that's being voted on? I don't want to be the author of this.

DR. SIEGEL: No, I understand that.

DR. MARCUS: We understand that.

[Laughter.]

DR. SIEGEL: Carol, why don't I have you restate your motion in a non-inflammatory manner, leaving out legal issues of mandate.

DR. MARCUS: Am I member of the public?

DR. SIEGEL: No, you're a member of the committee right now.

DR. MARCUS: Okay.

DR. GOODRICH: Mr. Chairman, who ever accused this lady of being inflammatory?

DR. SIEGEL: I do, often.

DR. MARCUS: Thank you, Mr. Chairman.

My non-inflammatory motion is as follows: The Advisory Committee on Medical Uses of Isotopes recommends to the Nuclear Regulatory Commission that no quality-assurance or quality-management rule of any kind is needed or appropriate.

DR. SIEGEL: I think that's a clear motion. Is there a second?

DR. GOODRICH: I second that motion.

DR. SIEGEL: Okay. We discussed this at length yesterday, but is there further discussion of the motion as framed?

[No response.]

DR. SIEGEL: Okay.

CAPTAIN BRINER: Move for the question.

DR. SIEGEL: The question has been called. We're going to do a roll call vote.

Dr. Marcus?

DR. MARCUS: Yes.

DR. SIEGEL: Dr. Pohost?

DR. POHOST: Yes.

DR. SIEGEL: Dr. Herrera?

DR. HERRERA: Yes.

DR. SIEGEL: Ms. McKeown?

MS. McKEOWN: Yes.

DR. SIEGEL: Captain Briner?

CAPTAIN BRINER: Yes.

DR. SIEGEL: Dr. Griem?

DR. GRIEM: Yes.

DR. SIEGEL: Dr. Goodrich?

DR. GOODRICH: Yes.

DR. SIEGEL: Dr. Collins?

DR. COLLINS: Yes.

DR. SIEGEL: Dr. Webster?

DR. WEBSTER: Abstain.

DR. SIEGEL: Dr. Almond?

DR. ALMOND: Abstain.

DR. SIEGEL: And the chairman takes his prerogative of not voting on a motion that has already passed.

The motion carries. The vote is eight in favor of the motion, two abstentions.

Let's, then, move on and let Dr. Alazraki make her statement.

DR. ALAZRAKI: Rather than making any kind of formal statement, I want to take the opportunity, first, to thank Mr. Glenn for making some clarifications here of the interim rule and ask for a few more clarifications on behalf of practitioners out there who still have questions which I find difficult to answer.

The understanding is that the interim final rule with regard to package insert instructions covers preparation of radiopharmaceuticals -- not administration or use of the radiopharmaceutical, just preparation. Therefore, although Dr. Silberstein included this in his report, is the six-hour rule included or not? Is it

supposed to be part of the interim rule reporting requirements, et cetera, or is that part of the use of radiopharmaceutical not covered by the NRC's authority?

DR. GLENN: I guess unfortunately that is one of the issues that is a part of the Syncor negotiation.

DR. ALAZRAKI: So there's no answer on that.

DR. GLENN: There is no answer on that.

DR. ALAZRAKI: Okay. When there is an answer, how will we know what the answer is?

DR. GLENN: I'm trying to think of how it can be resolved in the context outside the pharmacies. I think it may be resolved with respect to pharmacies.

DR. ALAZRAKI: Perhaps there could be a follow-up to the letter which you addressed to SNM and ACNP back in January when there is an answer to that specific question, with the understanding that any inspection or site-visiting individuals would also understand that an answer to this was not available for a significant period of time.

Second question: What exactly is the responsibility of the individual user versus the commercial radiopharmacy when deviations were apparent within the radiopharmacy but may not have been told to the user, in terms of reporting?

[Discussion off the record.]

DR. GLENN: I'm not sure -- Well, Larry says he's

going to get to that question later. There is one thing that your question raised that I have not clarified at this point, and perhaps that would help. When there is a physician-directed departure, the departure is made by a central pharmacy, the way the rule reads, it is the central pharmacy that is responsible for the record-keeping and the documentation of the reasons for the departure, and not the individual institution.

DR. ALAZRAKI: Then if we do a survey of the users out there, we wouldn't get that information.

DR. GLENN: If they use central pharmacies, that's correct. Again, that gets us right into the heart of the negotiations that are going on.

DR. ALAZRAKI: Okay.

MR. CAMPER: Let me just add to that, if I may, Dr. Alazraki. When we talk a little bit later this morning about the practice of radiopharmacy, as we look at the remaining issues in the petition, one of the questions that I'm going to be exploring is this concept of, when the pharmacist chooses to initiate a deviation, to what extent should a physician be made aware of that activity. We're going to be looking from some input on that from the committee, in fact.

DR. ALAZRAKI: And a third question: You discussed the difference between broad licensees and, say,

specific licensees, and you discussed that deviations could be permitted under some broad generic statement, let's say, in the procedure manual of a specific user on the type of procedure or radiopharmaceutical, and a generic type -- Does that apply to a specific licensee, where there's no committee to approve such a procedural manual change? Or does he have to go to --

DR. GLENN: It does apply to any licensee. They can do it for a procedure or for a radiopharmaceutical.

DR. ALAZRAKI: So a specific user could write that into this procedure manual without getting permission from central NRC that he can go ahead and do this.

DR. GLENN: That's correct. He must maintain the records required by the interim final rule.

DR. ALAZRAKI: Okay. I think, with the questions which you answered in your initial presentation, that answers, with the exceptions of the ones we couldn't answer, most of the --

DR. GLENN: There's a very specific one about the six hours.

DR. ALAZRAKI: Right.

Secondly, I'd like to just address the question of additional data that Mr. Cunningham raised vis-a-vis Dr. Silberstein's report. As Carol Marcus indicated, Dr. Silberstein feels that to get the type of specific numbers

that Mr. Cunningham indicated would be helpful would be a lot of work. If you think in terms of a three-year process for NRC to gather that work and the cost involved to NRC, perhaps, in that, you might want to consider a funding mechanism to SNM to do it in a matter of a few months. If Dr. Silberstein had some funding support, I think he could organize a data collection mechanism of specific licensees -- not broad licensees -- to get you the data in an expeditious manner. Usually when we think about grant funding, we think, What is the street value of this information? Is it worth that to do that? I think, since the NRC is the agency that is asking that question, that's for you to decide. I'm not sure that, in the context of what we know, we would feel it was worth it, but to us it certainly would be worth it to shorten this whole process and get on with it.

DR. SIEGEL: Let me just ask a procedural question, either of Mr. Cunningham or Dr. Morris. Is there a mechanism to obtain an NRC contract or an NRC grant if you all do not let the request for proposal? In other words, will you evaluate an independently submitted request for contract or for grant money?

MR. CUNNINGHAM: Yes.

DR. SIEGEL: So I actually suggested as much, I think, at the last meeting: that that was a mechanism that

the Society could pursue to provide funding to get the data, which is to make a scientific proposal for a contract or a grant to do this data-gathering. I suggest it again.

DR. ALAZRAKI: The committee might want to consider -- SNM and ACNP have already requested that this be withdrawn, and I think, in light of the potential, when it materializes, of an ongoing data-collection process by SNM to provide the data, that adds and enhances the propriety of that request.

DR. SIEGEL: I'm not sure I follow what you just stated.

DR. ALAZRAKI: Well, I think it makes the request easier for NRC, perhaps, to accept, given the fact that the data that they want will be collected -- or is being collected and will be submitted in short time.

DR. SIEGEL: Dr. Marcus?

DR. MARCUS: May I just point out that, up until 1987, there was absolutely no demand to follow the package insert, and millions and millions and millions of departures occurred. It is not as though departures are new because of this interim rule. Millions have occurred for many, many, many years. Before we really ask NRC to come up with money for a data collection when the practitioners of nuclear medicine are going to have to pay for that study, I think it's really important to understand what NRC would do wish

such data and whether it is really necessary to gather it anew, when one can look at what has happened for so many years and realize that no problems have occurred.

DR. SIEGEL: Okay.

Dr. Webster?

DR. WEBSTER: When we were discussing this a little bit earlier this morning, I think I heard somebody say that, when community hospitals were asked whether they had any deviations from package insert, they all said no. You said that they were scared silly, and therefore they had more reason to say no. Now, when this data-collection scheme is in progress, will they still have none, or will they say they have some, irrespective or the NRC attitude?

DR. MARCUS: I think of a radiologist out there in private practice who does a little bit of nuclear medicine along with everything else, and like most physicians he has no real knowledge of deviations that a centralized radiopharmacy might make, because all he cares about is that he gets a drug that works. I mean, that's what physicians always ask pharmacists for: drugs that meet USP standards, and that's it. How they get there none of us really care about, so he won't know.

DR. WEBSTER: Let me ask another question, then. Will the nuclear pharmacists be included in this survey?

DR. MARCUS: I think the nuclear pharmacist is the

most important person in the survey.

DR. WEBSTER: I didn't hear that before. I thought you were talking about --

DR. MARCUS: I mean, if you want to know what goes on, ask the people that do it, who are trained to do it, who are licensed by their states to do it.

DR. WEBSTER: All right. Thank you.

DR. SIEGEL: Do you have another comment?

DR. ALAZRAKI: Yes.

If the SNM was to design a study, yes, it would include the specific licensees and, if they used a radiopharmacy, the data would be gotten from the radiopharmacy.

DR. WEBSTER: Thank you.

DR. SIEGEL: It can be done if you want to do it.

Sharon, did you wish to make a statement? For the record, announce who you are and who you're representing.

MS. SURREL: Yes. Thank you very much. I am Sharon Surrel. For the record, I am the chairman of the government relations committee, Society of Nuclear Medicine, technologists' section.

I am sorry that I could not be here yesterday to hear the discussion on the QM rule; however, I would like to have it on the record that we oppose the QM rule in the technologists' section in its entirety. We are glad to see

that the majority of the medical advisory board also opposes this rule. As far as the interim rule is concerned, the question that it under discussion now, the technologists' section is very deeply concerned with the issues that are involved with this particular rule, and I can tell just from this morning that we do have some confusion as to what is going on with this rule. We would like to try and follow this a little bit more carefully before we make any statement with regard to the rule.

DR. SIEGEL: Thank you.

Okay. At this juncture, we should move on to discuss the additional issues pertaining to the SNM/ACNP petition, and Larry is going to give us an overview first, and then we'll probably break and get the specifics after coffee.

[Slide.]

MR. CAMPER: Thank you, Mr. Chairman.

The way I'd like to proceed with this particular part of the program is to give you an overview of the remaining issues in the petition, as we view them, at least, at this point in time, and, as part of that process, to share with you the language the staff sent to the Commission when we outlined the general plan for how we were going to deal with these remaining issues.

Also, primarily for the benefit of the audience, I

will go through six questions, I believe it is, that are contained in your briefing booklets under the section called "The ACNP/SNM Petition."

What I would like to do, after giving you the overview, is to rejoin you at the table and then to go through those questions and infuse those questions under each category as appropriate and ask some other questions, and I'm sure that Dr. Glenn and/or Mr. Cunningham may have some questions and points to make as well.

Let me try to set the flavor for where we were on these issues and try to convey to you what we're trying to achieve here. We do not come to you on these issues with some pre-established position. We are not coming to you in the manner that we did with regards to the QM rule in January. We are not prepared to go line item by line item on the staff version of language. We are much, much earlier in the process than that.

One of the things the Commission has asked us to do with this committee is to have this committee involved -- and the agreement states also involved -- earlier in rulemaking processes. For that reason we come to you early on. There is a danger in that. There is a danger in the sense that we can ask you questions that are general in nature, that we may or may not get feedback that is specifically relevant to the task at hand. When we come to

you without prepared position, it really is a wide-open scenario, but that's okay, because we view ourselves at this point in time as somewhat of a sponge, if you will, on this particular issue. The issues that confront us now are complex; they're interrelated. In some cases, as with radio-labeled biologics, they are emerging technologies, and we want to try to get the best information that we can from this committee.

We're really not here today to debate whether or not these are the remaining issues in the petition. We're really not here to debate whether or not we have the right approach. We are really formulating the approach, so please, as you structure your comments and your input, keep that in mind. We are looking for constructive input. We are looking for your help early on to guide us in this process. Clearly, over the next three years we are going to be interacting a great deal with FDA. We intend to use our medical visiting fellow, Dr. Rotman, who's a radiopharmacist, as you know, for a lot of input on these issues. It's very fortunate from a timing standpoint that he'll be with us. We'll be working closely with Dr. Morris's group, the Office of Research. It's going to be an involved, complex process, and we are involving you early in the game.

Please bear that in mind as you offer comments.

[Slide.]

MR. CAMPER: Just briefly, the process, as you might recall: We had told you last time that we were going to go back to the Commission by November of 1992 with what we're going to do with the remaining issues in the petition. This could result in a proposed rule, or it could result in a denial of some portion or all of the petition. I think it is fair to say that the last, I think, is unlikely to occur. I think certainly, generally, up through management at Mr. Cunningham's level, we genuinely believe that the remaining issues in this petition need action. We feel that there is a need to continue the process that we initiated as part of the interim final rule. We do believe that there is a need to address issues associated with the practice of radiopharmacy, radio-labeled biologics, and human research. I suspect that what will come out of all this will be some type of rulemaking that's proposed to the Commission by the staff.

[Slide.]

MR. CAMPER: What are those remaining issues? The use of radiopharmaceuticals for human research, the use of radio-labeled biologics, and compounding of radiopharmaceuticals from reagent chemicals. What I will do, if you'll bear with me, is, I will read to you just briefly the information that the staff provided to the

Commission in a Commission paper on each one of these categories.

With regard to human research, "Currently part 35 addresses the administration of byproduct material only for diagnostic and therapeutic procedures, not for research use. An amendment of this type and nature to part 35 potentially would permit all types of medical licensees to conduct medical research using byproduct material. The potential impact to public health and safety from such an amendment would need to be assessed. Furthermore, if research is added to part 35, all existing part 35 requirements on diagnostic and therapeutic uses would need to be reviewed and, if needed, revised to avoid potential overlap or ambiguity."

With regard to the radio-labeled biologics, the staff said the following: "In FDA terminology, the PLA for a biologic is similar to a new-drug application for a pharmaceutical. Currently no PLAs have been approved for radio-labeled biologics, and 10 CFR part 35 is silent on the use of radio-labeled biologics. Before an amendment is considered for part 35 allowing general use of approved PLA radio-labeled biologics, the staff should address potential new radiological safety core concerns associated with the preparation of radio-labeled biologics. The iodination and preparation of radio-labeled biologics requires more

handling in the medical laboratory or pharmacy than the current use of sodium iodide, and, thus, greater potential for exposure for occupational workers exists. In addition, radio-labeled biologics can involve the use of alpha emitters and, of course, high-energy beta emitters. This would result in radiological risks for workers that are not currently present in the use of pharmaceuticals in the practice of nuclear medicine.

"The staff believes that specific quality-assurance procedures for the preparation and use of radio-labeled biologics may be required. For example, it is important that the patient be correctly identified, because there is a potential for great harm to the patient if certain radio-labeled biologics are given to the wrong patient. In particular, in the case of monoclonal antibodies, an antigen-antibody reaction may preclude future diagnostic studies or therapy for that patient. Therefore, specific, redundant identification procedures might be required for these patients as a use of radio-labeled biologics."

With regard to the compounding of radiopharmaceuticals from reagent chemicals, we said the following in that Commission paper: "Currently, part 35 allows compounding if it is part of an FDA-accepted IND protocol. Also, part 35 allows pharmacies to perform the

final stage of radiopharmaceutical preparation using kits for which FDA has approved an NDA. Whether compounding of non-NDA or non-IND radiopharmaceuticals should be allowed may depend upon the route of administration, the radiopharmaceutical, or the radionuclide involved. Resolution of this issue will also require research to define the potential safety concerns, the minimum training and qualifications requirements for nuclear pharmacists, and the quality-assurance procedures to be followed by nuclear pharmacies. Extensive discussions with the FDA, state boards of pharmacy, and other national organizations will be needed on this issue."

So those are the comments that the staff made to the Commission as we outlined our broad plan with the following issues. Now, what I will do now is go through the questions that are in your book, of which there are six, so that everyone will be familiar with them. When we commence the discussion, what we will do, as I said a moment ago, is, we will infuse those specific questions under each one of these categories. I think that would be the most orderly way to do this so that the staff can go back at a later time and use this transcript as part of the process as we develop the rulemaking.

With that in mind, what I'll do is show you those questions that all of the committee members had in their

booklets.

[Slide.]

MR. CAMPER: We're asking, What is the availability of organizational and professional standards with regard to the training and experience of individuals preparing or compounding radiopharmaceuticals, generators, or reagent kits. Also, with regard to production and compounding facilities and with regard to quality requirements for final products.

[Slide.]

MR. CAMPER: We're going to ask, What is the role of the FDA package inserts in determining how radiopharmaceuticals are prepared and what can be added or deleted during preparations. I suspect we'll get a fair amount of input on this one. We certainly hope so.

[Slide.]

MR. CAMPER: We're going to ask, What is the role of the radiochemist in developing and preparing radiopharmaceuticals.

[Slide.]

MR. CAMPER: This is an important question, we believe. When would you expect a radiopharmacy to initiate departures from package inserts in preparing radiopharmaceuticals? If they did so, how much information should the radiopharmacy give the clinician about the

pharmacy-initiated departure?

[Slide.]

MR. CAMPER: What are the existing organizational and professional standards or guidelines dealing with non-medical human research? In this case the term "non-medical" may be a bit of a misnomer. In this case "non-medical" means those research activities which do not provide a direct diagnostic or therapeutic benefit. We do recognize, of course, that a great deal of the human research that goes on does provide such benefits, and we try to draw a bit of a distinction there.

[Slide.]

MR. CAMPER: Finally, we'd like to know about the processes and procedures for insuring the safety and efficacy of non-IND and non-PLA radiopharmaceuticals. We'll talk about that specifically what we talk about the role of IRBs and RDRCs.

For the audience, who may not be familiar with those terms, RDRC is radioactive drug research committee, and the IRB is the institutional review board.

As I said, we will infuse these questions in under each of these three major categories, as well as some other questions that we have. Of course, we welcome general input, general commentary, or specific questions that the committee members may have as we go through each of these

topics.

DR. SIEGEL: It seems to me that, in terms of the way you've framed the remaining issues of the petition, you really have perhaps left out what is really the fundamental issue of the entire petition, and that is, what is the prerogative of a medical practitioner and his or her professional counterpart, the pharmacist, to practice their professions?

Now, I understand the regulatory framework under which part 35 is structured is based on the following concept: The concept is, NRC admits to itself that it has no expertise in review of the safety and effectiveness of drugs, and therefore defers to the Food and Drug Administration for issues that pertain to marketed products. In the process of so doing, the NRC goes a step further and assumes that the practice of medicine and the practice of pharmacy, insofar as they involve drugs, is limited to those activities expressly authorized by the existence of a new drug application or a PLA by the Food and Drug Administration. That's essentially the framework that forms the basis of part 35. I may be oversimplifying in some areas, but that's pretty close to the truth.

I think the fundamental question of the petition is, what is the prerogative of the physician to practice medicine and the pharmacist to practice pharmacy, as allowed

expressly by Congress as it framed the Food, Drug, and Cosmetic Act. I think the way you frame the question skirts the issue. The notion that the interim rule addresses the physician's prerogative is really only partial, because it only has partially addressed the physician's prerogative.

Another question that probably should have been on your list is, does radiopharmacy exist as a profession? That's a question that needs to be answered, and I know it's one you want answered, but I think it explicitly needs to find its way onto your list.

MR. CAMPER: Well, we appreciate those comments, Dr. Siegel. I think that some of the specific questions that I intend to ask under different of these broad categories, I hope, will get at the essence of that, because understand the task before us: We have been requested in this petition to make some fairly dramatic and sweeping changes to the language of part 35 as it relates to what physicians and/or radiopharmacists could do in the practice of medicine or radiopharmacy. Part of our process, if we are to consider making changes of this nature and this magnitude, is to gain a better understanding of that very question. While the specific questions that we asked -- those six questions -- one of those is not included in that list, it certainly is to be discussed under this broad umbrella, particularly with regards to the practice of

radiopharmacy.

I have a couple of very important questions that we need to understand, from a clinician's viewpoint, about the practice of radiopharmacy, that will help us as we consider what modifications are appropriate to part 35 as it relates to the requests in the petition.

So you're absolutely on the mark. I mean, the real question here is the prerogative of physicians and pharmacists under the practice of medicine and pharmacy and to what degree -- and what understanding do physicians have of just what the pharmacist may do within the normal practice of pharmacy. So we intend to get at those issues, hopefully.

DR. SIEGEL: Now, we're going to take a break in a moment here. When we come back, I'd like to begin with the issues that deal with research, because they seem to me to be in many ways the most uncontroversial, and we can provide you with very straightforward information about how that really works and what rules are in place. Since Dr. Webster has to leave a bit early and has knowledge, as a member of a radiation safety committee and an IRB and an RDRC, I'd like to have him here for that discussion.

I would also like to leave us, before we break, with a concept that I've put forth many times before in discussions with the NRC, publicly and non-publicly, and

that is that, as you think about this and as the committee talks about this, remembe that the vast majority -- the vast, vast majority -- of physicians and the people who work with physicians who practice nuclear medicine and radiation oncology do so with the best interest of their patients in mind. What they do is motivated because they want to take care of sick people as well as they can -- not because they wish to maximize their profits, but because they want to do what's best for the patients. They do so in an environment which requires that the cost of medical care be kept A'ARA. There is no argument that the cost of medical care must be kept as low as reasonably achievable in this society in which we currently live. Every time we turn around, HCFA takes another 10 percent out of reimbursement for radiology and nuclear medicine and surgery. If the things that the NRC, on the one hand, does are adding 10 per·ent increments while reimbursement is going down, you create unique pressures. But remember, even though those economic overtones are there, that's not what drives what physicians do. I believe that in my heart of hearts and know it to be true: that that's what we're there for.

With that little philosophical note, it's time for coffee, and we'll come back and deal with research.

[Recess.]

DR. SIEGEL: I think we should resume the

proceedings. As I said before the break, I'd like to begin with what I think is the simplest component of the questions that have been posed to us, and that is to deal with the research issues and understand the framework under which research is currently regulated in the United States as it involves byproduct and non-byproduct material.

Let me begin by making a few general comments about how the NRC might think about research that's done with radioactive drugs. This is a topic that is dear to the hearts of many of us in this room. Dr. Marcus, myself, and Dr. Goodrich were all involved in one capacity -- and Captain Briner -- or another with the FDA, as members or consultants of its advisory committee at the time that the transfer of authority for certain radioactive drugs occurred from the Atomic Energy Commission to the FDA, the first part in, I guess, 1972 and the final part in 1975, and were involved in that time in helping FDA draft and clean up the ultimate language of the radioactive drug research committee regulations, which dealt with a major component of research using radioactive drugs.

In addition, I'm a chairman of a radioactive drug research committee. Are you, Ted?

DR. WEBSTER: Yes.

DR. SIEGEL: Ted's a chairman of a radioactive drug research committee.

CAPTAIN BRINER: I'm on one.

DR. SIEGEL: Captain Briner's on one, and others of us here, I think, have experience with this.

As Dr. Jones can tell you, I've been pretty vocal about some of these issues over the years at radiopharmaceutical advisory committee meetings, and I think I have a reasonably good understanding of some of these issues.

One can imagine research involving four tiers of drugs. The four tiers of drugs that are used in the research setting are FDA-approved radiopharmaceuticals used for approved indications in the research setting -- and a simple example of that might be technetium-labeled red cells used to perform gated blood pool imaging where the information may or may not be of direct benefit to the subject but is primarily being done because some other drug's effect is being evaluated in the setting of patients with acute myocardial infarction. That's one type of straightforward research, and at the moment I think most part 35 licensees would think that they can do that research. The rule may say otherwise, but I think most of them would think that, with IRB approval, they would be able to do that research. They may be wrong, but I think they would think they could.

The next step up the complexity ladder is the [illegible]

of an approved drug for a non-label indication, an unapproved indication, in a research setting. For example, if we go back just a few years, the use of technetium-sulphur colloid for gastric emptying studies in a setting where you wished to find out what effect domperidone -- I'll spell that for your later, transcriptionist -- has on the rate of gastric emptying in patients with diabetic gastroparesis. One can conceive of many other such uses of approved drugs for unapproved indications that would fall initially in a research setting and then ultimately evolve their way into clinical practice.

The third step up -- and in some ways this is not necessarily the order in which it goes, but tends to be the order of complexity -- is the use of drugs that are governed under the regulations in 21 CFR 361.1, and those are the regulations that describe the functions of radioactive drug research committees. Radioactive drug research committees are institutional committees that are specifically authorized and approved by the Food and Drug Administration pursuant to the regulations of 361.1, and those committees are authorized to approve certain drugs for research use -- drugs that have not been approved by the FDA -- and they are allowed to do so, even though the drugs might be conceived of as being new drugs, because of an interesting legal trick that's built into the language. That is, the drugs that are

used in that research setting are defined as generally recognized as safe and effective for the research purpose and therefore exempt from many of the provisions of the Food, Drug, and Cosmetic Act if the meet the following criteria: The criteria are that the drugs is known in the dose to be administered not to product a pharmacologically detectable effect in human beings. The implication of that knowledge is that there is in fact some human experience with the drug. Discussions leading up to the formation of that rule and the preamble to the final rule made it clear that FDA understood that there was the issue of technetium-labeled aspirin is not really the same as aspirin, but for all practical purposes it would be assumed that tacking technetium onto aspirin wouldn't change the pharmacology of aspirin. That's been the operating posture, even though I think pure scientists recognize that that may not always be a true statement. But it has been an operational statement. So pharmacological effects.

The radiation dose had to fall within specific limits, and those limits were, for a single administration of the drug, 3 rems to bone marrow, gonads, whole body, and lens of eye -- which doesn't make much sense, but that's another story -- and 5 rems to any other organ or tissue; and, for multiple administrations of the radioactive drug or for a combination of multiple radioactive drugs, either a

total limit or an annual limit of 5 rems to the critical things that I just mentioned and 15 rems to any other organ or tissue.

So a radiation dose limit, a pharmacological dose limit, and then some general provisions that the RDRC has to ensure, and those are that the study is one designed to obtain information about basic biochemistry, physiology, or panthophysiology. That can be broadly interpreted, but the important provision is that the study performed under an RDRC's purview is not intended for immediate diagnostic or therapeutic benefit of the research subjects and is not intended to substitute for a formal IND-regulated clinical trial if the intent is to gain data about the safety and effectiveness of a drug that might ultimately be marketed.

I forgot to include a point about the use of in pediatrics. The use in pediatrics is basically allowed, but the doses are adjusted by a factor of 10, and the RDRC's deliberations have to be aided by the advice of pediatric consultants called to assist the RDRC. IRB approval is required, and the RDRC is required to make a judgement that the information to be obtained by the study is scientifically important data and can be obtained with the study design as proposed, so that it will not be frivolous radiation exposure.

There are reporting requirements to the FDA that

pertain to dose and chemical quantities of the drug, and this is a mechanism that is extant in a substantial majority of medical schools in the United States. I don't know the total number of approved RDRCs, but at last count my recollection was it was in the range of 140, or something like that. Eric, can you --

MR. JONES: Close to 160.

DR. SIEGEL: Okay. Close to 160. I knew that ours is RDRC number 122, so I knew it was at least larger than that at one point in time.

That's what the RDRC does.

The next step up is when one wishes to do either a formal clinical trial to evaluate the safety and effectiveness of a radiopharmaceutical, to use a radiopharmaceutical in a research setting where in fact one is intending that there will be immediate diagnostic or therapeutic benefit to some of the research subjects, or -- and this is where there has been some controversy in the minds of many RDRCs -- where the entity that one is going to introduce into human beings is in fact a new chemical entity for which there is no prior human pharmacological experience. That, perhaps, has been the grayest area in the hands of many RDRCs -- that and what constitutes a clinical trial.

In that setting, what you do is what you would do

for research with any other drug. You file an IND, and that INC can either be physician-sponsored or it can be manufacturer-sponsored -- in the latter case, most often because that's down the path to getting the drug approved as an ultimately marketable radiopharmaceutical; in the former case, it will more often be motivated by the needs to do pure scientific research for intellectual reasons, but with an entity that it not otherwise approvable by the RDRC because of dosimetry or because of pharmacological limits, or because the purpose of the study is outright diagnostic or therapeutic at the front end.

Now, it's my understanding that part 35, as currently written, effectively precludes -- would allow specific licensees to use drugs that are covered by an IND in accordance with the protocol specific by the manufacturer or the physician sponsor. It probably would allow use of an approved drug for an approved indication for research. It probably would also allow use of an approved drug for an unapproved indication; presumably the radiation safety committee and the individual licensed would have looked at that, but it's part of the general allowance that physicians can use drugs for unapproved indications. But at the moment a specific licensee would not be able to use drugs under RDRC approval, and that that's a clear anomaly in the regulations. Broad licensees are often, these days, being

required to have RDRCs, which may or may not be a correct interpretation of the purpose of the RDRC -- I've understood that that has come up on several licensing reviews in recent years -- but a specific licensee might not be allowed to perform activities under the approval of an FDA-approved radioactive drug research committee.

DR. GOODRICH: My recall of this is that indeed, at the time the RDRC concept was developed, it was developed in order to provide a mechanism to allow the FDA to recognize that such a thing as a broad license existed, because the alternative to that was to remove the category of broad license, 3 to 83 atomic numbers, and convert everything to essentially the specific license, with FDA staff having to serve the functions that ultimately were returned to the broad licensees through the RDRC mechanism.

DR. SIEGEL: Actually, FDA wouldn't have had any real role in that. From the FDA's perspective -- and Eric can clarify this if he chooses to -- the major role that was served by having RDRC regulations in place was for the division, then, of oncology and radiopharmaceuticals not to be buried in INDs for all, at the time, tritiated compounds and C-14-labeled compounds that might be used in pharmacologic research. Now, things change, as the movie title points out, and RDRCs have become central in the pilot investigations and continuing investigations of

positron-emitting radiopharmaceuticals that are used in the research setting, and in a large number of institutions have become the starting point for many research studies at the front end of new technetium-labeled compounds where some link to human pharmacology can be shown -- there are some clever approaches to showing that these days -- but that really was the primary purpose. The existence of broad-license institutions that were doing research under AEC approval, I think, was not really the fundamental motivation for creating the RDRC regulations.

Bill?

CAPTAIN BRINER: I agree with you. Also, very much in FDA's at that point in time was that every single hospital, or maybe even every single medical school, should not have, necessarily, an RDRC, or would not be required to have one.

DR. SIEGEL: It's voluntary.

CAPTAIN BRINER: But the use of a single RDRC by several entities was encouraged, as a matter of fact. Several different hospitals, for example, or medical centers, use the same RDRC if they can make such arrangements. That would be in keeping with the part of the regs which would not permit -- would not be in keeping with the reg that says specific licensees can't use an RDRC.

DR. SIEGEL: Well, they don't say that they can't.

CAPTAIN BRINER: Well, they don't permit it.

DR. SIEGEL: They don't explicitly permit it. If you read the way the rule reads, it sort of implies that, if you're not using an FDA-approved drug or a drug under an IND, you're using a drug you shouldn't be using. The anomaly is that it clearly is FDA's intent to see RDRC-approved drugs used in the research setting with no questions asked -- assuming that all the rules pertaining to the RDRC are being met.

DR. GLENN: Let me make a clarification there. Again, part 35 is just totally silent on this issue. It neither authorizes nor prohibits. In fact, if you look at the scope of part 35 at this point, it covers only medical use, and this is not part of the definition of medical use that's in part 35.

But we do have non-broad, specific medical licensees who do come in and request this kind of activity. If they have access to an RDRC, that can be approved in a line item on the license, but it's an approval that would be under part 30 rather than under part 35.

DR. SIEGEL: Then let me backtrack to what I was saying about using approved drugs for either approved or unapproved indications in the research setting. Is part 35 silent on that, as well?

DR. GLENN: I'm not sure we've faced that issue

directly. It has always been our feeling that an approved drug for an approved indication certainly we didn't have any problem with.

DR. SIEGEL: Even if it's research and not for medical diagnosis or therapy.

[Discussion off the record.]

DR. SIEGEL: If I've framed this incorrectly, it's important that we get this out in the open.

[Discussion off the record.]

DR. MARCUS: Mr. Chairman?

DR. SIEGEL: See, it says -- Well, under subpart (e), if we just talk about imaging for a moment, 35.200, use of radiopharmaceuticals, generators, and reagent kits for imaging and localization studies. "A licensee may use any byproduct material in a diagnostic radiopharmaceutical or any generator or reagent kit for preparation and diagnostic use of a radiopharmaceutical containing byproduct material for which the Food and Drug Administration has accepted a notice of claimed investigational exemption for a new drug (IND) or approved a new drug application (NDA)." The governing word here that needs clarification is "may use," and the important term is, what is the purpose for which they may use it. If they may use it only for medical research -- or medical diagnosis or therapy, then research is in fact prohibited for specific licensees. If they may

"use it," not further defined, then research is permitted.

Carol?

DR. MARCUS: When the petition was written, it was felt that, as Dr. Glenn said, part 35 is silent on research, and one of the suggestions in the petition was to add it. If you look at the petition and the wording suggested, it simply added that whole category. Mr. McElroy said it was necessary because, as you said, the regulations were silent on that aspect.

DR. SIEGEL: Here's the definition of medical use. Used clearly in this case, it means medical use. Medical use, as defined in the definitions in 35.2 of part 35 is as follows: "Medical use means the intentional, internal or external administration of byproduct material or the radiation therefrom to human beings in the practice of medicine in accordance with a license issued by a state or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico." So the next question is, is performing medical research something that is licensed by being a licensed practitioner?

DR. POHOST: But it says the practice of medicine.

DR. SIEGEL: But who, other than a physician or an osteopath, can do medical research?

DR. POHOST: No, that's true, but, again, it's the practice of medicine encompassed when it says -- does it

encompass research?

DR. SIEGEL: So that really becomes the issue, in terms of whether part 35 is a little too silent about research.

MR. CAMPER: For fear of getting into the legal interpretation -- obviously we have to have our OGC do that -- we have heretofore handled limited specific licensees' requests for human research on a case-by-case, amendment basis, under the assumption that part 35 is silent on human research.

DR. SIEGEL: Dr. Collins?

DR. COLLINS: We've been using this term so lightly. Where is the dividing line between medical practice and research? In fact, what is research?

DR. SIEGEL: Well, that's not so easy to define, but that's what IRBs are for. It's known that it's often difficult to define. All of us who are physicians perform clinical experiments in the practice of medicine all the time when we break new ground in trying to do something innovative for a patient who has got a particular problem that we haven't quite tackled before. That's generally not conceived of as being research. On the other hand, when one performs a study in an organized intellectual framework, where the purpose of the activity is to gather information, and along the way the things you are

doing to the patient may or may not be of benefit to the patient -- that is generally conceived of as being research, rather than medical care per se.

MR. CAMPER: Let me use this opportunity to ask one of the questions that I had in mine, in view of this particular discussion. In the petition that was submitted to us by the ACNP/SNM, in part of their discussion they suggested a definition to be added to part 35 to cover the topic of human research -- or medical research. Their definition read as follows: "Medical research use means the intentional, internal or external administration of byproduct material or the radiation therefrom to human subjects for research purposes." My question to the committee is, does that cover all of the issues associated with human research?

DR. HERRERA: May I make a comment?

DR. SIEGEL: Sure.

DR. HERRERA: To follow on Dr. Collins, I hope in our infinite wisdom we do not destroy one of the most important things in medicine from the very beginning, which is to try to decrease the level of uncertainty in which we practice. That is research. That's how research started, in Greece, in medicine. That has always been an integral part of the practice of medicine. As I said, I hope that in our infinite wisdom we do not destroy that principle.

DR. SIEGEL: Mel?

DR. GRIEM: It seems to me, Dr. Siegel, you definition of medical research is too restricted. An epidemiologist reviewing death certificates and writing a paper on this disease or that, that's medical research. It seems to me that we need the help of some legal experts in regard to how you make this definition, and that you don't restrict someone with this license or that. It seems to me that the pharmacist, in doing something and coming up with something, be it in animals -- or the veterinarian -- is doing ultimately research. I think you also plan to assess non-human radiation devices, and so forth, which we talked about yesterday, should be in the medical research definition.

DR. SIEGEL: Mel, I think all we're talking about here is the application material to human beings in medical research.

DR. GRIEM: Okay.

DR. SIEGEL: I mean, I agree with you that medical research -- To take the broadest view, when asked a question -- for example, what is nuclear medicine research -- the answer is, Any research done by a nuclear medicine physician is nuclear medicine research. And medical research is any research done by anybody who is a physician or anybody who is allied in any way with the practice of

medicine -- any kind of research, including basic physics, can ultimately be conceived of in that framework as medical research. But what we're talking about here is whether or not use of byproduct material in people or on people is allowed or not allowed by part 35, and should it be allowed?

DR. HERRERA: May I make another comment? This reminds me of something that happened in my laboratory almost 40 years ago. We were interested in looking at circulation in the brain when we did a brain scan. At that point in time, we had to request a special permit that, in the patient that we were going to study for diagnosis of possible brain tumors, we could look at perfusion in the carotid artery with a probe.

Also, we were using Rose Bengal to study liver excretion, and we wanted to study the clearance of this material from the circulation by using the probe in the head, and we had to get a special permit. I think this is ridiculous. Here we are using approved drugs for a specific thing, but we cannot look at other aspects of the distribution of this radiopharmaceutical in the body? How ridiculous can we get?

MR. CAMPER: Are there any specific recommendations -- The language that I read, as I say, was the language proposed by the ACNP/SNM. Are there any specific recommendations to embellish that language,

restrict that language -- any other, additional thoughts in that regard?

DR. POHOST: Would you reread it?

MR. CAMPER: I will.

"Medical research use means the intentional, internal or external administration of byproduct material or the radiation therefrom to human subjects for research purposes."

If I may, I think it would be wise to read how that would then be inserted into 35.100, 35.200, and 35.300, as proposed in the petition. It would read, "A medical institution --" -- This would be added to those parts. "A medical institution licensee may use, for medical research use, any byproduct material in a radiopharmaceutical, and for use involving measurements of uptake, dilution, or excretion, if its use has been approved by the radiation safety committee (RSC) and the institutional review board (IRB) chartered in accordance with 45 CFR part 46." Clearly that example pertains to 35.100. There is similar language in 35.200 and 35.300.

DR. SIEGEL: I would argue that that definition in that regulatory text really adequately covers what needs to be covered within the existing regulatory framework of research that's already there. There are pretty specific regulations put forth by both the FDA and the Department of

Health and Human Services that pertain to protection of human subjects in the research setting, and the IRB role there is clear.

MR. CAMPER: One point I would make, if I may, is that the definition, as proposed, is silent on RDRCs. It mentions radiation safety committees; it mentions IRBs; it does not mention RDRCs. Is that applicable, appropriate?

CAPTAIN BRINER: It could be that their function is already well-established under food and drug law, as a matter of fact.

MR. CAMPER: Well, so are IRBs, for that matter. What I'm saying is, should it be included?

DR. SIEGEL: Yes.

DR. WEBSTER: Yes, I think so, because if you don't mention it you're silent on it, and people might say, under the NRC, part 35, you're not allowed to do this. Since RDRCs are well-established and a lot of institutions have them are actually using radioactive drugs under the RDRC, then you should acknowledge that fact. That's what I'm saying.

DR. SIEGEL: You're actually not going to run into a big problem. It's going to be a relatively small number of specific licensees that are going to have radioactive drug research committees. I think you need not worry that specific licensees are going to run out and form RDRCs in

any large number that will be approved by the FDA in any large number, once they read the regulatory text of 21 CFR 361.1. RDRCs don't give you broad license to go out and use anything you want for any purpose you want. They have incredibly specific restrictions in terms of what one may use under the purview of an RDRC in a research setting. The motivation of specific licensees to use things for those purposes is going to be very, very small indeed. Broad licensees are going to be far and away most likely to have any significant component of research under RDRC approval.

Carol?

DR. MARCUS: Your point about mentioning the RDRCs is very good. It is mentioned in all the statements of consideration, of course. Basically I think the idea was to include the umbrella of the regulations of the Department of Health and Human Services. Instead of detailing exactly what they are -- and if they ever change them, then you have to go back and redo your regulations -- what we had conceived of was to simply have you tie it to the regulatory framework of that agency, and then, if FDA changed or another branch of HHS changed, you wouldn't have to be stuck with this incompatibility again.

MR. CAMPER: I understand.

DR. SIEGEL: Right, and that goes back to my original statement of what really constitutes the framework

of the petition. The framework of the petition is that there appears to be now a component, large or small, depending on the area that you touch on, of dual regulation, where NRC regulations appear to be incompatible with the license provided physicians and pharmacists by their states and the regulations under which they operate from the Food and Drug Administration or DHHS, and the whole purpose of the petition is to try to bring those things into compatibility, so that there's not some specific loss of freedom for nuclear medicine physicians by comparison with other physicians.

MR. CAMPER: Right, and the approach, of course, is to specifically identify those mechanism -- IRBs, RDRCs -- and their regulatory context.

DR. SIEGEL: Okay.

MR. CAMPER: Another question that I h , if I may --

DR. SIEGEL: Sure.

MR. CAMPER: You did an excellent job of summarizing the research categories. The question that I was going to ask is, are there any research activities going on that there not covered by the obvious -- the IND, the NDA, the RRB, the RDRC. I think you've done a very good job of summarizing that, so I don't think we need to belabor it.

The other question, then, that we had on the list

of questions was, existing organizational and professional standards or guidelines dealing with medical human research -- can we summarizing that in a minute or less? You've talked a great deal about FDA. Are there any other comments that would seem appropriate in terms of guidelines or standards dealing with human research?

DR. SIEGEL: By that you mean who can do it?

MR. CAMPER: Who can do it, professional standards, organizational standards.

DR. SIEGEL: Well, I think my first-line answer would be that the framework that's in place and the framework that the regulatory text of proposed amendments -- or petition to 35 suggests is there to assure you that the standards will be met. First of all, our radiation safety committee approval is mentioned there as a requirement.

IRBs are specifically empowered by HHS and/or FDA to do their task, and institutions file a set of general assurances with the Department of Health and Human Services that indicate the procedures they will follow and a long list of agreements that they have to follow about how the IRB operates. I can assure you, you can't get an IRB approved that's composed of country bumpkins who don't understand what research is about. People who sit on IRBs have to have training and experience that allows them to be on IRBs, as well as having a broad representation of the

kinds of interests that need to be on an IRB, which includes laypeople, includes people with backgrounds in medical ethics, as well as the people who have the scientific background that would allow them to make the scientific judgements. IRB membership also requires that some of the folks who sit on the IRB not work for the institution that sponsors the IRB and have no fiduciary relationship with the institution in any way, the point being to make sure that there's some independent, non-cajolable voice on IRBs. So the IRB rules build an awful lot of protection in for human research subjects.

The RDRC mechanism, if followed properly -- and I hope Eric would tell us that most RDRCs play the game by the rules -- in many ways, it is easier to file an IND and proceed to do your research than it is to do research under an RDRC. The RDRC rules are restrictive. The reporting requirements are actually a little more arduous than you might need for certain very open-ended physician-sponsored INDs. Then the RDRC is a committee the membership of which is specifically approved by the Food and Drug Administration. The institution doesn't say, These are the people on the committee, and just go about its business; the FDA has to approve the members of the RDRC.

Eric, did you want to comment on that?

MR. JONES: All that you're saying is very true

and accurate. I can only reinforce the difficulty that sometimes people encounter when they want to go through an RDRC rather than the IND mechanism. The RDRC is an exemption to the act for the IND, and it is generally more defined. When we get an IND in, we actually get to see the protocol. Frequently with the RDRC we may only see the name of the research, and on occasion I have requested that the investigator at that institution submit the protocol, so that we can be sure that there's no diagnostic or therapeutic intent. But certainly it is difficult to face the RDRC and the IRB together.

DR. SIEGEL: Thank you.

Carol?

DR. MARCUS: Just one more point to address Mr. Camper's question about existing standards: When the RDRC regulations were written, one of the standards that he to be set was radiation absorbed dose to the human subjects. The standard that was used for that was yours. We started with part 20 and the radiation absorbed dose for workers, and that was the guiding standard for the FDA as they put together their regulation, so you in fact were sort of indirectly -- or really directly -- the standard-setting body for that portion of the RDRC.

DR. SIEGEL: Yes. It was assumed that subjects participating in research were taking on some additional

risks akin to those that an occupationally employed individual might take on.

Ted?

DR. WEBSTER: I think there are several other points about the RDRC which ought to be recognized. The first one is that there are some mandatory members of RDRCs. One of them is an expert in dosimetry. The other one -- very important -- is an expert in the pharmacological aspects. In our institution, we work very closely, as members of the RDRC, with the pharmacy committee, who also gets to have a look at these proposals, in terms of purity, for example, and other aspects of quality.

The second point, I think, is that an important part of these RDRC proposals -- and, in fact, all IRB proposals -- is that there must be informed consent. The informed-consent part of the protocol is looked at very carefully to see that the description or the assessment of hazard is fair and is informative to the subject, who is typically a patient -- not necessarily, because you also have normal volunteers involved in these procedures.

I think the RDRC has a rather narrow orbit, and some of the other -- Initially, when we had an RDRC, which goes back to 1975, the RDRC did everything, so to speak, with regard to unusual and research procedures. Since then, we have involved the radiation safety committee in giving

approval for some of the things that Dr. Siegel mentioned -- f · example, the first two items on his list, which is when a radiopharmaceutical is used as part of another investigation, the assessment of efficacy of drugs, for example, where you might want to use a radiopharmaceutical to evaluate the efficacy of the drugs. That now goes through the IRB and the radiation safety committee, and there's interlock, as there is, I think, in most of these institutions: an interlocking between these various committees.

For an unapproved indication, the application is made, but it doesn't go to the IRB; it goes to the radiation safety committee -- in our institution -- who uses its authority, if you like, to assess the reasonableness of the new approach.

I would like to say something perhaps a little bit adverse about the dose limits for research, though. They have been around since 1975, and there is no mention of ALARA, so to speak, in these regulations, in part 361.1. There are limits, though, and the limits are actually the annual limits that have been mentioned for occupational exposure. Since these are -- I'm looking to the future now -- likely to be changed -- in fact, the ICRP has already changed in their latest publication, publication 60; they've already come down to, effectively, 2 rems per year,

whole-body dose, no more than 10 rems in five years. That may eventually, I guess, have some impact on the RDRC regulations, although I've never heard any discussion of that, up to this point.

DR. SIEGEL: I don't have the text in front of me, but it's my recollection that the RDRC regulations do make a statement that, in the process of making its judgements, the RDRC should consider that the radiation exposure shall be no greater than necessary to obtain the scientific information, which is a way of including the ALARA statement. My recollection of the preamble to the 1975 rule is that that was discussed in detail and made eminently clear.

I mean, I agree with you entirely that one should not view the RDRC regulations as a basis for taking license to give 15-rem doses in all research settings to the spleen whenever you get the chance.

DR. WEBSTER: That was just my point.

DR. MARCUS: Remember, though, that everything that goes through the RDRC, which is the FDA arm, has to go through the radiation safety committee, which is your arm, and ALARA is very definitely there.

DR. SIEGEL: That's not necessarily true. I would point out that different institutions have chosen to skin the cat in different ways. As Ted points out, the radiation safety committee in their institution takes over some of the

functions of the IRB for certain types of research protocols, and that, I'm sure, is part of their assurances to DHHS to indicate that that's going to be their procedure. At Washington University, the radioactive drug research committee reviews every proposal that involves radioactive materials, whether it's 21 CFR 361.1-regulatable or not, but takes over, in the process of so doing, some of the functions of the radiation safety committee, and does so by specific statement in our license that indicates that that's the way we do business.

I would simply point out that, in any given institution, there will be an IRB, a radiation safety committee, and potentially an RDRC, and that some sharing of responsibility as part of an institutionally specific plan will have been worked out and will, by perforce in the case of a license, have been made part of a license condition, in all likelihood; and, with HHS, if it's an institution that gets any kind of funding from the federal government, will be laid out in the assurances to HHS.

CAPTAIN BRINER: Just to prove to you that Duke does things other than play basketball, the same committee serves both functions at Duke. The RDRC serves as the radiation safety committee, so we see it from both sides of the street.

DR. GLENN: I seek one clarification, or set of

advice, from the committee. The discussion seems to definitely focus on having this done in an institutional setting with these committees available. I guess one of the questions would be, do we need in our regulations explicitly to say that this should be done in institutions; can it be done in private practices? Or would requiring these committees to be involved essentially take care of that?

MR. CAMPER: That's an excellent point. Let me just add to that, if I may, one thing I think might be helpful to the discussion. That is, in the language that was proposed by the petitioners, the definition of medical institution was described as follows: It "means a single health-care facility or a health-care organization which may physically exist in multiple, separate locations but is integrated through economic and/or management agreements. Several medical disciplines may be practiced in a medical institution." With that in mind, Dr. Glenn raises a very good questions.

DR. SIEGEL: Was the text written such that research could only be performed in institutions?

DR. MARCUS: That was not the intent at all, but the assumption was that a single practitioner, if he really wanted to do research, had a lot of hoops to jump through, certainly, by borrowing an IRB, borrowing an RDRC. In California the regulation is that you have to have an

institution with such committees adopt you before you can do it in the context of private practice.

DR. SIEGEL: Correct. That really is the truth. The link to certain federal regulations if you accept any federal funding. It is conceivable that an independent practitioner can do certain kinds of research independent of oversight by an IRB; however, that physician then violates the Helsinki doctrines, which govern what all of us do and spell out quite clearly what the obligations of medical practitioners are when dealing with subjects in research settings.

Now, an independent practitioner can in fact do research but would have to get -- and I think it would generally be acknowledged that this is true -- approval of an IRB, or, if it involved byproduct material, approval of some radiation safety committee, or approval of an RDRC, and I can tell you Carol describes it quite correctly: a lot of hoops to jump through, because most IRBs -- One of the functions of an IRB is not only to approve the research, but to monitor the research. That is required by 21 CFR and also by the HHS regulations. If a guy doesn't have any fiduciary relationship with you, it's hard to monitor what he is doing, and therefore a practitioner will basically have to say to an IRB, I give you permission to come in and inspect what I'm doing, before most IRBs would accept that

responsibility.

This is not going to be a problem for you. You're not going to have independent office practitioners who are trying to do things in a research setting. For example -- Jerry may tell me otherwise -- I can't imagine a manufacturer going to a small, private nuclear cardiology group that's independent of an institution, wanting to have that be a site for a phase 2 or a phase 3 clinical investigation.

DR. POHOST: Not by itself.

DR. SIEGEL: They want to do this in the setting of an organized health-care institution where (a) they've got all the assurances and (b) where they've got the resources necessary to put the research package together.

I think you need to think about the language, to make sure you've covered it adequately, but it's kind of a non-issue.

DR. MARCUS: What we were thinking about is, for example, you have attending staff in medical teaching institutions who are physicians in private practice, many of whom are of excellent caliber and give their time, for free, to the institution for teaching purposes, and who like to be involved with the intellectually more exciting, dynamic aspects of practice. Many of them have previously been on the staff of that teaching institution but have gone off

into private practice. The feeling is that they could ask the institution to take responsibility for this project in an oversight sense in exchange for the services they render as attending staff.

As Barry says, it's very rare, but it does happen once in a while. I know of just I think two instances. Certainly the quality of the people was beyond anyone's reproach in terms of professional capacity.

That was what was meant in the coverage here.

DR. POHOST: But these people are under the jurisdiction of the institutional review process.

DR. MARCUS: Absolutely. The rad health in Sacramento will say, I will not accept the radiation safety committee of Mt. St. Elsewhere because it's composed of the one guy who does the work there, so you will have to borrow the radiation safety committee of the University of St. Elsewhere if you're going to do that work. I think that's a reasonable assurance of a good review.

MR. CAMPER: The only remaining question that I have is question number 6, which is the process and procedures for ensuring the safety and efficacy of non-IND, non-NDA, and non-PLA radiopharmaceuticals. That question lends itself to topic 1 and topic 3, but I think, as far as human research is concerned, we have probably covered it pretty thoroughly with the discussion of the IRB and the

RDRC. I really don't think there's much we can add to it; or is there?

DR. SIEGEL: And in the setting of a broad license, the radiation safety committee takes on that responsibility for reviewing those things. In the setting of research, efficacy is probably not an issue, because you don't know efficacy, necessarily.

Now, in the setting of RDRC, you do know efficacy, because it's defined as being efficacious for that research purpose. That's legally now. That's the whole reason that you can get an exemption from the requirement of the acts. It's safe and effective for that specific purpose.

Okay.

MR. CAMPER: Dr. Glenn or Mr. Cunningham, any questions on this topic?

MR. CUNNINGHAM: No.

DR. SIEGEL: Where do you want to go next?

MR. CAMPER: Let's go to number 2. Let's go to the radio-labeled biologics. Does that work?

[Discussion off the record.]

DR. SIEGEL: We're going to deal now with the broad question of what constitutes the practice of radiopharmacy; what is it that radiopharmacists do for a living; how does what radiopharmacists do or not do differ from what technologists do or do not do under the direction

of physicians in institutions that don't have a radiopharmacist? We might touch on a little bit about what radiochemists do in institutions that don't have a radiopharmacist and how that differs from what radiopharmacists do, if it does at all. And that's enough to keep us busy until lunch time.

MR. CAMPER: The question, just to restate the question that I had one the slide, was, should nuclear pharmacies, institutional or commercial, be allowed to compound radiopharmaceuticals, and all that that implies?

CAPTAIN BRINER: Where is that question?

MR. CAMPER: It's in the slide --

DR. MARCUS: We're going to make you legal.

MR. CAMPER: That's right. We're going to make you legal, finally.

[Laughter.]

DR. GOODRICH: The state of North Carolina made him legal. When we appeared before the board of pharmacy, he and I together, to explore --

DR. SIEGEL: Use the microphone.

DR. GOODRICH: Bill remembers well, when he joined my group at Duke, we went before the North Carolina board of pharmacy, a group of very reasonable, intellectual individuals, and explored with them the need, or the perception of need, that there be something different about

our radiopharmacy from Eckert's or Drexol or whatever. It was there determination that a pharmacist is a pharmacist is a pharmacist. He is licensed; he has, by peer review, proved his expertise, and under the laws of the land in the great state of North Carolina the responsibility for licensing has been imbued upon the pharmacy through the pharmacy act, and we did not have anything that was different or constituted a practice that was a deviation, to use NRC's terms, from the practice of pharmacy which is covered by the laws of the land.

My concern, which I have to raise here -- and I must again and again -- is the need for all of this. Dual regulation is a prominent issue before Congress at this present time. I think, as a matter of fact, that FDA is concerned about dual regulation in the context of the EPA threats, real or imagined. I think at this point in time we have a very clearly defined regulation and a regulating body, the FDA, and the states -- the respective, sovereign states -- for the regulation and the management and the oversight and, if need be, the militant enforcement of the practice of medicine and the practice of pharmacy.

From what origin does this festering wound arise to cause the NRC to go through all of these convulsions when it is being done and being done very clearly and very well. If they need further definition, then all they have to do is

go to the sovereign states. I think California has set a very excellent precedent, and we know of that. California is almost as big as Pennsylvania in square feet, if not a little larger. I have to raise my voice to say, Why? What has prompted this?

MR. CAMPER: The comment to Dr. Briner was clearly a joke. We obviously don't legalize him. We recognize the sovereignty of the state of North Carolina and all the other 49 states.

DR. GOODRICH: Let the record so show.

[Laughter.]

MR. CAMPER: The reason for the discussion, of course, is to look at ways in which the part 35 might be modified to address some of these issues. You have raised a very ideal opportunity to ask the first question, if I may.

We often hear that the state boards of pharmacy control the practice of radiopharmacy. A problem that comes to mind potentially is that NRC regulates some 20-odd states, 22, 23 states; therefore, there are 22 or 23 different state boards of pharmacy. There seem to be inconsistencies amongst those state boards of pharmacy. The question for the committee, then, would be, what types of standards or ways could be looked at by NRC to approach what appears, at least, to be inconsistencies amongst the state boards of pharmacy and what they require in the practice of

radiopharmacy, given that we have to develop regulations that would cut across a number of state boundaries?

DR. SIEGEL: Well, one simple answer would be, none -- based on the assumption that, if the system isn't clearly broken, do not fix it. That's one answer.

Let me partially answer the question by again giving a little framework here and talk about a law which is a work of art. That is the Food, Drug, and Cosmetic Act. It is a law that gives the FDA pervasive powers to regulate the use and flow of drugs in the United States, but also gives them the latitude to lay back and let practitioners -- and I include both physicians and pharmacists -- to do those things they judge to be in the best interests of their patients -- or, if you will, their customers -- based on their professional judgement. FDA has the authority to come in and stop physicians or pharmacists from doing things if they recognize an imminent danger to the public health and safety, but it's an authority they don't often exercise in that setting, because of my starting premise, before the break, which is that physicians generally do things that are motivated in the best interests of their patients, and pharmacists generally do things that are motivated in the best interests of their customers.

So the FDA regulatory framework provides physicians who don't use radioactive drugs with the

flexibility to use marketed or non-marketed products with a fair degree of latitude. When one gets into very non-traditional uses, which have the potential to do harm, even those products that are developed by an individual pharmacist in his own laboratory, FDA has tricks for coming in and shutting that activity down, even though the interstate commerce provisions never occurred, but FDA rarely has to do that, because of the fact that bad abuses do not often occur.

Now, there are other things that apply here. There's another portion of this regulatory framework, and this is that the United States Pharmacopeia Convention publishes a big book that's full of monographs, and that monograph is a compendial standard, and it has the force of law. For the many -- I think now it's about 60 -- radiopharmaceuticals that are in there, if you do not comply with the compendial standards for those radiopharmaceuticals, you are distributing or making a product that can be considered to be either adulterated and/or misbranded under the Food, Drug, and Cosmetic Act, and there is a strong regulatory framework already in place for shutting you down. The state board of pharmacy can shut you down; your state medical licensing board can shut you down; but the Food and Drug Administration also can shut you down.

Now, the USP standards, the Food, Drug, and Cosmetic Act, are linked to a system that is primarily related to the marketing of drugs in interstate commerce and don't necessarily, except with these unusual exceptions that I just laid out, get to the issue of what happens on the day-to-day basis in the physician's office or in the local pharmacy down the block. State boards of pharmacy and state medical licensing boards have a greater degree of responsibility for dealing with those things when problems arise and for doing the licensing up at the front end.

What the NRC regulations do, as they currently stand, is tie practitioners -- physicians and pharmacists -- to a document that the FDA never intended to be one that has the force of law, namely the package insert. The package insert -- and I don't want to get into this prematurely -- represents a summary of -- I'm going to put this word in quotes -- best -- in quotes -- available scientific information concerning the use of the drug. Now, the best available in many instances means the information that was made available. The way the package insert initially gets formulated is, a manufacturer who's going to sell a drug submits the information necessary to prove the safety and effectiveness of the drug to the Food and Drug Administration, along with a proposal about how that drug should labeled. These are the claims that the manufacturer

wishes to make about the drug, and that information is all laid out in the label. The FDA sits down and carefully looks at the scientific evidence presented in the application, as well as other scientific evidence that might be available from the world's literature and from experience in other countries, where such exists, to determine that the claims in the label are in fact justified, based on the scientific data that are available.

That information is then provided to the practitioner with the understanding that, if the drug is used in accordance with the label, the practitioner has a reasonable right to expect that the drug will behave as described in the label. FDA has made it very clear in both information notices to physicians, and in fact in a Federal Register information notice some years ago, that the package label was not a document that prohibited practitioners from extending beyond the bounds of the information in the label. As the question has been framed by the petition, all nuclear medicine practitioners are asking for is the right to do with their drugs what other physicians can do with the drugs that they use, recognizing that their motivation for so doing is going to be based on the fact that they want to do something for a patient that they otherwise wouldn't be able to do.

DR. GOODRICH: You're using the terms "package

labeling" and "package insert" interchangeably.

DR. SIEGEL: Correct.

DR. GOODRICH: Let the record so show.

DR. SIEGEL: Go ahead.

DR. MARCUS: I think one of the things in the petition that's sort of important was a discussion of what the term "unapproved use" means. I think that the FDA's choice of term was probably confusing to people who were not intimately involved with the FDA process. Many people thought that an unapproved use was the same thing as a disapproved use. FDA, I think, has understood that and now frequently refers to these as unlabeled uses rather than unapproved uses, to distinguish the fact that they are not disapproved at all, but are simply not uses that FDA is prepared to make any judgement on, because it has no data.

I think the use of the term "unlabeled" will be better than the term unapproved. I encourage its further use. We got into one amusing situation the other day where I was going to a committee for an unlabeled use of an approved product and my chairman said, No, no; it's a labeled use of an approved product, because you're putting a label on it -- a radioactive label. I said, No, no; that's not what it means. He said, Yes, I know, I know, I know.

But, aside from the confusion of that use of "label," I think one of the purposes of the petition was to

clear up the use of the word "unapproved use."

MR. CAMPER: Let me steer us, if I may, for a moment away from the package insert issue, although this is very helpful, because there are a couple of crucial questions about the radiopharmacist that we have a need for input on.

Given that state boards of pharmacy license pharmacists, we have an interesting dilemma that we face, as a regulatory agency, in licensing of radiopharmacies, and it goes something like this. In that process, for a commercial radiopharmacy to obtain a license, there must be at least one licensed pharmacist. However, other individuals are designated as authorized users under a radiopharmacy license, and for all intents and purposes go about the practice of radiopharmacy. They may do this under close supervision or varying degrees of supervision, but the dilemma that faces us -- and the question that I would ask is -- should all authorized users on a radiopharmacy license be licensed pharmacists?

DR. MARCUS: It's very similar to the situation with physicians and technologists. Pharmacists may use technologists, and the state pharmacy law sets the limitations for how much work may be done by technologists. The pharmacist is always responsible for the end product, just as, when a physician has a technologist helping prepare

drugs, the physician is responsible for the product.

MR. CAMPER: But there is a less-than-subtle difference, in the sense that these individuals, as authorized users on a radiopharmacy license, will be compounding radiopharmaceuticals and perhaps producing new products that don't have INDs or NDAs. Technologists don't do that.

DR. SIEGEL: Let me just pose a question. Is it necessary that you name these individuals as authorized users, or could they be supervised individuals?

MR. CAMPER: Interesting question. They certainly could be that. Currently we authorize users on a radiopharmacy license.

DR. SIEGEL: So that anyone who's compounding the drugs is named on the license specifically as an authorized user?

MR. CAMPER: That's correct.

DR. SIEGEL: So every employee is a radiopharmacy is an authorized user?

MR. CAMPER: Not every employee, no. There are individuals who, by virtue of training and experience, are requested as authorized users on a radiopharmacy license. They, however, may not necessarily be a licensed pharmacist.

DR. SIEGEL: All right. Then why not just take that to its logical extension in subpart (j) and define the

training and experience necessary, one of which would include certification by some licensing board, to be an authorized user on a radiopharmacy license.

MR. CAMPER: That's a good point. Currently understand that we do have criteria that is radiation-safety oriented, similar, if you will, to that training and experience of a minimal nature which is required for authorized users that are not board-certified physicians. However, recognize, though, that all physicians who become authorized users are indeed licensed physicians in their state. Clearly the distinction, at this point in time, at least, is that there are authorized users who meet some minimum level of training and experience that we have defined that are not necessarily licensed pharmacists.

CAPTAIN BRINER: Let me interject something here. I'm not sure how it's handled in other states, but in North Carolina, on my permit to operate a pharmacy, and indeed a specific radiopharmacy in the State of North Carolina, I have to list everybody who is going to have anything to do with those drugs, including technologists who work in my lab or in my pharmacy. I have to list the other pharmacist or pharmacists that might be involved. The state board of pharmacy is perfectly cognizant every time I file a permit application or an amendment to that application. They know who is involved in the making of these drugs. I think

that's where the proper responsibility lies: with the state board of pharmacy.

The pharmacist still bears the responsibility -- I bear it -- for what goes out the front door of that pharmacy.

DR. MARCUS: I think many states, like California, have a law that says that no drug may be dispensed in a pharmacy unless a licensed pharmacist is present. It's even more restrictive than what goes on in physician institutions. The state law itself it enormously restrictive. I wouldn't worry about it, if I were you.

You know, really, there are enormous parallels between the regulations of pharmacy and medicine on the state level. They are very, very, very similar. The pharmacy law is very strict about the use of paraprofessionals, or whatever you want to call them.

DR. SIEGEL: I actually think that this is raising an interesting regulatory concept. That is, you are willing to allow licensed physicians who are named as authorized users latitude for supervision and latitude to make a certain number -- not necessarily all -- professional judgements in their use of byproduct material. A way to handle this for independent radiopharmacies would be to make licensed radiopharmacists -- or people with equivalent training and experience, so as to avoid that

restraint-of-trade issue that comes up with board certification for physicians -- authorized users with delegated responsibility to supervise individuals, such that the professional judgements that constitute the practice of radiopharmacy and would deviate from package labels are made by individuals who have the professional training necessary to make the judgements.

I mean, I would, for example, want to be very certain that we preserve the right for a physician who is in a practice that doesn't have a pharmacist to be able to lay things out in a procedure manual and set up a group of deviations that will be carried out by technologists but delegated, supervised, and ultimately the physician is responsible.

I think that the difference between a clear-cut medical, institutional setting right now and an independent radiopharmacy is that you solve the problem in an independent radiopharmacy by making a radiopharmacist responsible, as the ultimate authorized user in that setting. Now, if a pharmacy has got a half a dozen pharmacists, it can have a half a dozen authorized users, but still might have a dozen supervised pharmacy technologists who work under the direction of the authorized user and work from procedure manuals, so that I would no more let a nuclear medicine technologist make a pharmacy

judgement -- or a medical judgement; nor would I expect an authorized user in a radiopharmacy who is a pharmacist to allow a pharmacy technologist to make a pharmacy judgement, outside of the bounds of a procedure manual.

CAPTAIN BRINER: That's exactly the way it is.

MR. CAMPER: Right. And understand, again, we have no preconceived idea that they should all be licensed, but, in trying to understand the link-up with state boards of pharmacy's requirements and so forth, it's a worthwhile question.

Another question that was on our list --

DR. SIEGEL: Dick has a question.

MR. CAMPER: Oh, I'm sorry.

MR. CUNNINGHAM: This has been an important discussion, so I want to summarize it as I understand it --

DR. SIEGEL: Yes, sir.

MR. CUNNINGHAM: -- and perhaps go one step further.

With regard to radiopharmacies, what is being suggested is that the authorized user be identified as a radiopharmacist with some training appropriate for a radiopharmacist, in a manner similar to the way in which we license physicians as authorized users. The technologists, the paramedicals, what have you, the parapharmacists that work under these people are under the supervision of the

authorized pharmacist in a manner similar to that.

Now, where we have a -- I don't know if I can call it a pharmacy, but where drugs are being prepared under the direction -- there are physician-directed departures or physician-directed drug preparations --

DR. SIEGEL: Right.

MR. CUNNINGHAM: -- where a radiochemist is doing the actual preparation, in that case it would be under the direction and authorized use of the physician who supervises that radiochemist, but the radiochemist is responsible to the physician, who in turn is responsible for what happens under that license.

DR. SIEGEL: Correct.

DR. MARCUS: And the same if the chemist works for the pharmacist.

MR. CUNNINGHAM: Correct.

DR. SIEGEL: Right, and I think it unfortunately has to be, even though it takes a lot of very talented people and relegates them to second-class citizenship. There are some radiochemists out there who are perfectly capable of making all of the judgements that would be made by any licensed radiopharmacist, but, by tying yourself to the licensed practitioner, you have the clearest direct sight to the whole legal framework that governs the practice of medicine and the practice of pharmacy. The fact that

I've got Mike Welch, who is a former president of the Society of Nuclear Medicine, working in my institution, who could run circles around most radiopharmacists in terms of the judgements he would make about the preparation of a drug, is irrelevant, because Mike Welch understands that, when he makes a drug for me, I am taking the ultimate responsibility for what he does, and he therefore has to keep me posted about what he's doing that's outside of standard procedure.

I really think -- I mean, we don't have any radiochemists directly in the room at the moment, and there may be some who would be offended by this concept, but I think that that's the cleanest way for the NRC to get out of this quagmire.

MR. CUNNINGHAM: Yes. It certainly is the most clean way, so that we don't have to have various grades of people, trying to control various levels. It clearly is the cleanest way, and it fits in with a practice that is already in existence. Clearly is easiest. And, as I recall, when I was looking into this, there are some training standards for radiopharmacists.

DR. MARCUS: Well, not only that. There's board certification in nuclear pharmacy that is analogous to board certification in nuclear medicine.

MR. CUNNINGHAM: Yes, and that may be sometning

that we can recognize, board certification. There is a problem with that, in that I understand that the number of board-certified radiopharmacists falls far short of the demand for radiopharmacists.

DR. MARCUS: You can fix that easily.

DR. SIEGEL: Well --

MR. CUNNINGHAM: That may be.

CAPTAIN BRINER: Let me get in on this, Barry.

DR. SIEGEL: Yes, Bill.

CAPTAIN BRINER: The one thing you've got to remember and that everybody has to remember when you're talking about radiopharmaceuticals is that we're talking about prescription drugs. They all require prescriptions -- no over-the-counter stuff -- or under-the-counter stuff, for that matter.

DR. SIEGEL: But what Bill's saying is, as defined in the FD&C Act, these are prescription drugs.

CAPTAIN BRINER: That's exactly right.

DR. SIEGEL: These are not OTC products.

CAPTAIN BRINER: Now, in the loop of people who are responsible for the dispensing and use of prescription drugs, chemists do not appear. Under the law, pharmacists dispense drugs, licensed pharmacists. Licensed physicians use them. Now, there is an exemption for a physician to say, Okay, I'm going to have someone else prepare my drugs.

He can delegate that responsibility, as Barry said, but ultimately he bears the responsibility for what that guy or gal puts out.

If it's a prescription coming out of a radiopharmacist -- a radiopharmacy -- and I'll speak to that point too, in a second -- there is shared responsibility, because you've got two licensed professionals involved in this thing, and each of them is covered by their rights and responsibilities under that act and under the separate state practice acts, so you don't even want to comingle pharmacists and chemists in the same breath. They don't mix.

Now, the one additional thing I wanted to say: It is not sufficient for a pharmacist to be a licensed pharmacist to run a radiopharmacy in this loop. It must be a permitted pharmacy under the state board of pharmacy. In other words, it's a hospital pharmacy, if you want to look at it that way. My license in the state of North Carolina is exactly the same license as the Duke Hospital pharmacy has hanging on their wall. I have a permit to operate a pharmacy, which happens to be called the Duke Medical Center Radiopharmacy. So there's that additional thing in the loop.

DR. SIEGEL: Bill, just let me make sure I followed that last point. If a nuclear medicine physician

were to hire a radiopharmacist to work either in an institutional setting or in a private-practice setting but did not license it as a pharmacy, then the physician still has the ultimate responsibility in that sector.

CAPTAIN BRINER: That's correct.

DR. SIEGEL: The link is to the pharmacy license and having a licensed pharmacist running the pharmacist.

CAPTAIN BRINER: He'd be a lot better off having a licensed pharmacist work for him in that context.

DR. SIEGEL: Absolutely. That's the way I've got it set up. I have a couple of licensed pharmacists, and we are licensed as a pharmacy, in addition to having our nuclear medicine practice.

Tony had a question.

We'll clarify it, Dick, in a second.

Go ahead. Tony, for the record, announce who you are so the transcriptionist gets it.

DR. TSE: My name is Anthony Tse, T-s-e, from NRC staff.

Dr. Siegel, I just want to make one clarification from your remark. What you said, I understand it, is that a physician could direct a non-pharmacist to prepare any pharmaceuticals. Is that what you were saying?

DR. SIEGEL: Any?

DR. TSE: Any.

DR. SIEGEL: Yes. Correct. Under the Food, Drug, and Cosmetic Act, I believe that the physician has that prerogative.

CAPTAIN BRINER: It's under your medical practice.

DR. MARCUS: It's medical practice.

DR. SIEGEL: And under your medical practice.

DR. TSE: Let me, then, have a follow-up question. How do you determine what kind of standard a physician will use to determine which technologists have a sufficient expertise and training, such that they can do the pharmacist's job, or prepare something that you prescribed.

DR. SIEGEL: Well, in that setting the physician would be responsible for establishing the procedures and then making certain that the procedures are being followed, and making the professional judgement that the individual -- I mean, part of the whole regulatory basis that you all have of delegation is that you have made a judgement, as the delegator, that the individual to whom you are delegating the responsibility and whom you are supervising has the training and experience necessary to carry it out, has been adequately instructed, and that you review their performance periodically to assume that your instructions are being met.

I don't see any difference with a technologist preparing an unusual variation on a radiopharmaceutical than I see in giving a technologist instructions to do something

non-standard as part of a nuclear imaging procedure. It requires the same level of responsibility on my part that I made a judgement that I need something done as part of medical care, and it's in the patient's best interest, and, in order to get it accomplished, I'm going to have the following people who assist me in my practice do the job for me.

I don't think you need a special set of rules there. The rules you've got already make it clear that the authorized user and the licensee, when they don't do everything by themselves, have clear obligations to make sure that the people who work for them are doing it right.

DR. TSE: My point is not related to the rule. It's just for my understanding.

DR. SIEGEL: I understand that.

DR. TSE: I wonder whether there's any standard or something written down by which a physician can judgement whether the person who is not a pharmacist can do a job a pharmacist should do.

DR. MARCUS: He's not doing the job a pharmacist should do. The pharmacist doesn't have to get the physician's permission. The pharmacist is an independent professional. The technologist is obeying procedures that have been derived by the physician, or perhaps by a consultant nuclear pharmacist whom the physician has hired

as a drug expert to write these procedures, or perhaps the physician will say to use a package insert in lieu of any changes. The standards are the standards of the United States Pharmacopeia, whether the standards are met by the drug. In our practice, the standards are usually checked up on specifically by the images.

DR. SIEGEL: Let me answer the question this way: Let's say that the issue at hand is whether or not to deviate from a package label by adding ascorbic acid to a radiopharmaceutical, and then to do so henceforth and forever. That's a judgement that a physician could make, a professional judgement. That's a judgement that a pharmacist, working in an independent radiopharmacy, could make without a prescription from a physician to do so. That is not a judgement that a pharmacy technologist could make on his or her own; nor is it a judgement that a nuclear medicine technologist could make on his or her own. But, once the procedure had been put in place, the nuclear medicine technologist could do that as part of the routine procedure henceforth and forever.

Joan, do you agree with that?

MS. McKEOWN: Yes, I certainly do. I also want to say that we do have allied health professional standards. We have nuclear medicine technology certification boards. We also have a segment of the AART which certifies nuclear

medicine technologists. We have a set of practice standards which we have on file with the government that do include the preparation of radiopharmaceuticals under the direction of the physician.

I think that, as a technologist, I remember way before we had anything called a radiopharmacist. We are not doing what a pharmacist does. We are doing what we are directed to do with radioactive materials.

DR. SIEGEL: Correct.

Dick?

DR. TSE: Thank you.

DR. SIEGEL: Thanks, Tony.

MR. CUNNINGHAM: A quick question: The earlier discussion about licensed pharmacy and licensed pharmacist: When I was up here before I contemplated our rules referring to a person licensed by the state to practice pharmacy, as we characterized the position. Is there any need for us to be concerned about licensed pharmacies where these drugs are being compounded?

CAPTAIN BRINER: If they weren't licensed, they wouldn't be in business.

MR. CUNNINGHAM: But does that have any role to play in our rules? That's what I'm trying to sort out.

DR. SIEGEL: Let me go back to what I said earlier. Can a licensed pharmacist practice what is

conceived of as pharmacy in my employ if that physical locale is not also licensed as a pharmacy, or is he only doing my bidding as a physician?

CAPTAIN BRINER: It would depend entirely on your philosophy, Barry. If it were entirely on your bidding, then he could practice that way. He need not practice that way, if you told him, I want you to provide me the best drug you can provide for me.

DR. SIEGEL: No, I understand what he's doing professionally --

DR. MARCUS: He may be under the hospital pharmacy.

DR. SIEGEL: I'm asking about the issue from a state pharmacy law point of view, whether a pharmacy license is required for a licensed pharmacist to be doing what is considered the practice of pharmacy.

CAPTAIN BRINER: No --

DR. MARCUS: He can't do it in his garage.

CAPTAIN BRINER: No, but the instrumentality of a prescription cannot be used in that case. There must be a pharmacy in order to fill a prescription. You only have a pharmacy if it's permitted as a pharmacy by the state board of pharmacy.

DR. SIEGEL: Mark? Identify yourself for the record.

DR. ROTMAN: Mark Rotman. I'm a board-certified nuclear pharmacist, NIH, and maybe someday a visiting fellow at the NRC.

I've had my hand up so long it's practically numb.

DR. SIEGEL: Now, now.

DR. ROTMAN: I want to muddy the waters a little bit. I'm sorry, but this needs to be said.

In your practice, Dr. Siegel, when you order one of your radiopharmacists to prepare something, he prepares it and, I'm assuming, dispenses it, but that is different from administering it. There's a difference. I don't believe there are too many radiopharmacists that actually intravenous injections of the radiopharmaceuticals.

DR. SIEGEL: Correct.

DR. ROTMAN: So there is a slight difference that has to be looked at. The radiopharmacists prepare the radiopharmaceuticals. They dispense the radiopharmaceuticals -- sometimes, in my setting, directly to the patient and with the supervision of the physician oral things are administered. But the great majority are intravenous injections, and they are injected by someone qualified to do that, either the physician or the technologist, so the ultimate responsibility for the actual crossing of the skin boundary of the patient for the radiopharmaceutical belongs to the physician ordering it.

DR. SIEGEL: Unequivocally. No argument at all.

DR. ROTMAN: There's a different between the ultimate responsibility for the radiopharmaceutical and then maybe a lower responsibility, maybe, for -- if you want to call it the quality of the radiopharmaceutical.

Now, to push on a little bit, what we discussed a lot in the meantime, a pharmacy is something that's licensed by the state licensing, and that gives that licensed pharmacist in that licensed pharmacy the power to dispense prescriptions to patients. Now, we're all sort of tainted by, growing up, going to the corner drug store and getting a prescription filled, and the pharmacist actually hands it to you. For most non-radiopharmaceuticals, the pharmacist actually dispenses it, and the patient self-administers it. Very rarely, again, does the pharmacist actually administer the drug to the patient. On occasion I've had people with eye infections so bad that they had trouble getting the first dose of eye drops in, and I've helped them. I've had to teach people how to swallow tablet; M&Ms work real good for that, by the way. But most of the time the pharmacists are involved in the act of dispensing the medication, not administering the medication.

Now, to become a pharmacist, you have to go to pharmacy school. Almost everywhere in this country it is four years and involves a competitive state board

examination. It involves an internship. It is nearly analogous to going to medical school and doing your internship for that. I don't believe there are any pharmacists that are coming out of school today that went less than three or four years of pre-pharmacy before they could even apply to pharmacy school, so you're talking about an equivalent amount of education that most physicians get.

When you add radiopharmacy to that, now the situation gets a little more complicated, because -- Well, if you think about it, a long time ago physicians were physicians and surgeons; it said it right on their license. When they graduated from medical school, they could cut, if they wanted to. There really wasn't any regulation about going through a surgery residency or whatever.

DR. SIEGEL: There still isn't.

DR. ROTMAN: Well, it would be hard to find an anesthesiologist, maybe.

DR. SIEGEL: I'm licensed as a physician and surgeon -- God help the patients whom I cut on.

[Laughter.]

DR. ROTMAN: I'm trying to get to a point here that radiopharmacy has evolved one step beyond what we all think of as classic pharmacy. Probably unbeknownst to a large number of people, pharmacy is now evolving into a series of subspecializations. Radiopharmacy was the first.

We took our boards for radiopharmacy back in 1982, so we're almost talking ten years that it has been a recognized, board-certified specialty. Right now, this summer, there will be other board-certification exams offered in pharmacy, so there will be other board-certifiable specialties in pharmacy. For nine years I have been the only recognized specialty in pharmacy.

Just the same, a pharmacist by license does not make him a radiopharmacist.

DR. SIEGEL: And let me just point out that a physician by license does not an authorized user make. That's why there are training and experience criteria in subpart (j). I would propose that a board-certified radiopharmacist who is a licensed pharmacist would fall in just like an ABNM-certified physician.

DR. ROTMAN: Exactly.

DR. SIEGEL: A non-certified radiopharmacist would have to prove by training and experience that he has got what it takes to be an authorized user in a radiopharmacy.

DR. ROTMAN: Okay. Exactly. Now take that one step further, to the pharmacy, the licensed premises where prescriptions are filled. I could no longer elute my generator at the local People's drug store here and expect to make a radiopharmaceutical any more than the pharmacist at People's could fill prescriptions for tetracycline in my

radiopharmacy.

So radiopharmacies, licensed radiopharmacies, obviously have different physical requirements, instrument requirements, than regular pharmacies. In a regular pharmacy, you must have a certain kind of balance and a number of volumetric measuring devices so that you can pour out and weight out and do the things that you would do in normal compounding of prescriptions. Those things don't apply to radiopharmacy. We need dose calibrators. We might need digital electronic balances. We might need laminar flow hoods. There's a different set of requirements. An issue that needs to be looked at is, when radiopharmacies are licensed, do they have all of the requirements to operate safely that the NRC wants them to have.

Now, that may be the only issue in which the NRC can join hands with the local boards of pharmacy -- the state boards of pharmacy -- to perhaps set some sort of standard minimum requirements for a radiopharmacy to operate.

I have been practicing in a large federal institution for almost 13 years now, so I'm a little out of touch as to what really happens on an individual state board level. I will have to look into that, but I suspect that the state boards of pharmacy now recognize that there is a difference and have different requirements for a local

radiopharmacy versus a regular pharmacy.

DR. SIEGEL: We were able to get the state of Missouri, when we applied for our pharmacy license, to exempt us from the requirement for having a mortar and pestle.

[Laughter.]

DR. ROTMAN: Thank you.

DR. SIEGEL: It's 12:00. I'm sure there are lots of pregnant thoughts, but they'll be here after lunch. Let us adjourn for lunch and resume at 1 o'clock. I know most of us in the hotel also need to check out as well, so we'll see you in an hour.

[Whereupon, at 12:00 noon, the meeting adjourned for the luncheon recess, to resume at 1:00 p.m.]

AFTERNOON SESSION

[1:20 p.m.]

DR. SIEGEL: Let us resume our discussions. We're still on the same topic, the petition issues. Larry, why don't you tell us where you'd like us to head next?

MR. CAMPER: Okay. We have one or two, perhaps three, questions that we'd like to try to wrap up quickly, if we can. We've had a great deal of discussion about the latitude allowed to radiopharmacists to practice radiopharmacy, and we did have a question specifically in that area. It was, when would you expect a radiopharmacy to initiate departures from package inserts in preparing radiopharmaceuticals, and how much information should the radiopharmacy give the clinician about the pharmacy-initiated departure? As you answer this question, a resounding theme that keeps coming through that Dr. Glenn and I were talking about a moment ago is, we seem to be hearing that radiopharmacists do indeed have a wide latitude. I guess it would be helpful to know what the boundaries are -- I mean, short of obviously, criminal acts, et cetera -- but just some narrowing focus, if you could, on what those boundaries are.

DR. SIEGEL: Well, in the case of a drug that is listed in a compendium, the USP standards are the limit. If the product conforms to the USP standards then the drug is

within target.

CAPTAIN BRINER: Throughout its period of use.

MR. CAMPER: This is pharmacist-initiated?

DR. SIEGEL: Or physician-initiated.

DR. MARCUS: There are provisions in the FD&C Act where you can use a drug that does not meet USP standards, but, number 1, you cannot use the designation USP; number 2, it has to be clear to the pharmacist and physician why it doesn't meet USP standards. There are circumstances where you would use a drug in an emergency situation, usually, or for some reason why it's okay, but people have to know it's not up to standards.

MR. CAMPER: What about the issue of information available to the clinician when a pharmacist initiates a departure?

DR. SIEGEL: If the product that is being dispensed can carry the label USP, that is as much information as one needs to know that the drug will perform in accordance with the compendial standard.

MR. CAMPER: And if it doesn't? Does the physician need to be aware of the standard that was used if it is not USP.

DR. MARCUS: It is the USP standard.

DR. SIEGEL: No, he means in the case of something that doesn't conform to the standard. I would say probably.

But help me think of an example.

DR. MARCUS: Okay. Technetium gelfoam.

DR. SIEGEL: There's no USP standard.

DR. MARCUS: That's right. There's no standard. Usually a radiologist might ask a nuclear pharmacist to make up some technetium gelfoam because he wants to float some gelfoam into an obliterated or bleeding vessel, and he just wants to be able to know afterwards where it ended up, because gelfoam is not radio-opaque. He is going to trust, probably -- in our case what has happened -- that the pharmacist will give him a preparation that has a very degree of binding of technetium to that gelfoam, and then he might ask the pharmacist, By the way, what kind of binding do you expect, and he'll expect the pharmacist to say, Probably better than 95 percent, or better than 90 percent, something like that. You kind of assume he has been an appropriate professional and not giving you one with 80 percent unbound technetium.

DR. SIEGEL: The circumstances in which things that are outside compendia are used are relatively few, and they would be most often used in very specialized circumstances, where a physician requesting such a drug would have had reasonable close contact with the pharmacist who is preparing it for him, or would have decided on his own exactly how the drug is to be prepared, based on some

preliminary research, or there would be some reasonable documentation of the way that behaves in the literature before it was extended to the next pharmacist and the next pharmacist and the next practice. But there are relatively few of those kinds of things.

For example, now modified in vivo labeled red cells are actually in the package, labeled, for at least one of the pyrophosphate kits that is out there, but for the longest time in vivo labeled red called were made in a manner for GI bleeding studies that were not described in the package label, through a combination that involved activities both of physicians, technologies, and pharmacists working in concert. The reason people adopted those practices widely is that the literature made it eminently clear that to fail to do so would result in an inferior-quality study, and so you needed modified in vivo labeled red cells to do a gastrointestinal bleeding study. Protocols, several of which work but differ in some minor degrees one from the other, are available in the published literature that one can choose from to proceed to set up the procedure in an individual laboratory. What a nuclear medicine practitioner does is look at the literature, write a procedure that then is translated into practice either by the technologist working in that laboratory or the technologists and the pharmacists who serve that laboratory.

Gelfoam is sort of an extreme example of something that is not -- not extreme extreme, but something that's not very commonly used.

Technetium-labeled white cells might be another example of something where --

DR. MARCUS: There were no standards for that. There's the albumen colloid kit that you tag with technetium if you're going to use it for a phagocytic white cell label. There are not standards for that, but the standards essentially evolved from the people who did the research, who did quality control on the product, and learned what was possible, learned that that quality control was compatible with a good study, and published it.

There are other examples, I think, where you take an approved drug and radio-label it, when that approved drug was never meant for labeling in the first place. Therefore, although you take an approved drug and a technetium generator which is approved, the combination of the technetium on the approved drug has no standard for what percentage should be free or not. Then you use professional judgement. Probably someone writes a paper on it and says that, if you do it this way, this way, this way, reduce it with ascorbic acid, and get to this point, you should be able time after time to get about 95 percent, plus or minute 2 percent, labeling, and it appears to be stable over the

period of six hours or eight hours, or something, that we made it up. That is not a compendial standard, but it is a guideline that a professional would find very useful.

There are other situations where, unless I knew there was a package insert departure, I wouldn't use the product. For example, if Syncor said, we can get you sodium iodide exactly as it comes, NDA-approved, I'd say, Keep it, because I want them to add the stabilizers to prevent the volatilization. It's an enormous difference. Having had one action level in a technologist's thyroid with a product that was NDA-approved and not stabilized, I can assure you I was writing prescriptions that said, Not to be filled by a Syncor product until they promise to depart from the package insert and add thiosulfate EDTA.

The same with ascorbic acid. If I have a choice of bone kits from a company that puts ascorbic in versus not, I'm going to buy it from the guy who puts the ascorbic acid in, because I know that, if it takes me a while before I inject the patient, I'm going to have a better product and a better scan.

DR. SIEGEL: The generic answer to the question, when would you expect a pharmacist to initiate departures from the package insert, is, when such departure would be expected to make the product perform better in some way and be doing so within cost considerations that are ALARA.

Now, you might ask, appropriate, If you know that adding ascorbic acid to the vial makes it work better, why doesn't the manufacturer just go back and add ascorbic acid to the vial and get the FDA to approve that? The answer, at least as I've heard it said many, many times, is that that -- I don't see Eric anymore -- the cost of supplements to drug applications is judged by manufacturers to be sufficiently high and the risk that the entire file be reopened and eight million other things be identified is judged to be sufficiently high that manufacturers have made that the current system makes it too risky to make products better. That's a sad state of affairs, but it's perceived widely as being the truth. I've heard many drug companies make the statements, or their representatives make the statement -- and I believe it to be true, because I'd also said, Gee, why don't you just do this simple thing, get this change in the labeling, add this simple compound to the kit, and it will be a better deal, and they say, We just can't justify it economically, because it will be too difficult for us, too expensive for us, to do that.

On the other hand, a pharmacist, using his or her professional judgement, can make that improvement without running all the risks, if you will, of having the FDA open the file, as it were.

So, in a way, the pharmacist's activity is

skirting some of the FDA's supervision that you all value so much in terms of your regulatory framework, but it's being done for a very specific purpose that reflects on the reality of the modern world and how we practice within it. And it's done with a patient's best interest in mind and ALARA in mind.

The quality-control system that's out there is better than you think it is. If I order from a commercial radiopharmacy bone agents that every day have visualized the thyroid and stomach activity, I find out real quickly, and I either stop ordering from that source or the problem gets fixed. That's true of all the radiopharmaceuticals I used.

Does that address the question, at least partially?

MR. CAMPER: I think so.

DR. SIEGEL: Bill, did you want to add something?

CAPTAIN BRINER: No, that's fine.

DR. SIEGEL: Mark had a comment. He may make it.

MR. CAMPER: Mark, if you're coming to the microphone, I would ask that you help us within one of the other questions, which is question number 1. It said, the availability of organizational and professional standards applicable to training and experience of individuals preparing or compounding radiopharmaceuticals, generators, or reagent kits, production and compounding facilities,

quality requirements for final products. Perhaps some of the various boards of pharmacy, the association for that group, as well as SNP or ACNP -- you know, those types of things.

DR. ROTMAN: Let me make the comment I came up for first, and then we'll go to that, because it took you like 30 seconds just to read me the question, and I was still thinking of the first part.

MR. CAMPER: That's fair. Good. Go ahead.

DR. ROTMAN: The communication between the pharmacist and the physician, whether it be your retail pharmacist at People's and your general practitioner in an office or between your radiopharmacist and your nuclear medicine doc, is a critical element whenever there is something that needs to be communicated. In routine matters, when we make up bone agents, I can't think of too many times that the physician has asked, What percent bound is it, or, What's the pH of it? They're really not too concerned, because it's a routine product that's made every single day, and they're come to trust the level of quality.

When you leave that and go into what you guys like to call your standard deviations, when you get away from the routine products, then communication becomes critical. I make things -- radio-labeled antibodies -- that take me 8 to

12 hours to make for one dose for one patient, and I have a full page of information that I transmit to the physician after I've made it. It includes everything that you could possibly ever imagine, because there are so many variables.

What the physician needs to be told when the pharmacist initiates departure is going to be dependent on the product and the frequency with which that product is made, the circumstances. If it's 3 o'clock in the morning and you haven't got enough technetium to do it the normal way, then you might communicate different information than when it's new and it's a regular part of the working day. I think you need to understand that it's not a black and white subject, this communication thing, and to prescribe a regulation, that such and such will be communicated, is sure to miss some things that need to be communicated and force communication of things that don't need to be communicated.

I think that was said once already in the last day or two.

But go ahead. Would you read me the question again?

MR. CAMPER: I certainly will. In my haste to keep things moving along, I hit you with a tough one as you were walking up.

[Slide.]

MR. CAMPER: There we go.

I wonder if you would have a comment or two regarding the items in this slide.

DR. ROTMAN: Okay. For A, training and experience of individuals for preparing or compounding radiopharmaceuticals, generators, or reagent kits, that in itself requires a certain amount of explanation. For routine compounding of radiopharmaceuticals -- shall we say fully approved technetium products that are USP -- to make those obviously requires a lower level of competence than to probably describe the radio-labeling of white blood cells, and it would take even a higher level of training and experience to compound radio-labeled antibodies. PET radiopharmaceuticals are going to fall up in the higher end of training and experience. Again, that's not something that you can just say, Well, 200 hours will do it, or, 400 hours will do it. There are different things that require different amounts of training and experience.

[illegible]t of the training and experience requirements to become board-certified -- and you assume, and rightfully so, that someone who is board-certified can do all of the above that I just described -- those training and experience requirements are very carefully defined, outlined, and listed, from the board of pharmaceutical specialties of the American Pharmaceutical Association, which is the governing body for pharmacists in America.

I will make it a point to provide you with all of the board of pharmaceutical specialties' written information. There are nuclear pharmacy practice standards. There's quite a stack of things that are involved to become a radiopharmacist -- board-certified, that is.

MR. CAMPER: Thank you. That was helpful.

DR. ROTMAN: Okay.

For production or compounding facilities, now we're back sort of to that square where we talked about licensed pharmacies, requiring 32 square feet of counter space and adequate lighting and ventilation to store your drugs so that you can dispense your tetracycline and things, as opposed to a radiopharmacy, which needs different facilities. The facilities needed to function in a radiopharmacy are going to depend on what you do there. Minimum requirements are obviously well described in your model regulations, about having a dose calibrator and survey meter, a refrigerator. There are some things that are required, and I think that the list gets larger depending on what you do.

The quality requirements for final products are either described in your USP, if they're USP products, or in the procedures within your own institution. Lastly, if they're IND, they're going to be described in the IND.

I think that covers A, B, and C. do you have any

other questions?

MR. CAMPER: No.

Only if I can ask you ask you're walking back to your chair.

[Laughter.]

DR. SIEGEL: Does anybody want to amplify on that answer?

CAPTAIN BRINER: I think that's about as succinct as you can make it and quite correct.

MR. CAMPER: All right, then. I think that the only thing that I would ask in the final question would be, getting back to the role of the FDA package insert. A lot has been said about it. I think we're getting a clearer understanding of it with each passing comment. Would anyone on the committee care to embellish on the remarks that have been made already regarding the package insert?

DR. SIEGEL: Only that I think it's reasonably clear that the package insert is meant to be guidance, in the sense that it reflects -- it's a legal document in the sense that it reflects FDA's signing off that this body of information is supported by adequate and well-controlled evidence documenting safety and efficacy when the drug is used in this fashion. It is not, however, a statement that, if the drug is used in any other fashion, then it is not safe and effective.

That's an important distinction. Once can have assurance that technetium-mag-3 is stable up through six hours because the package label says it will be and USP says it will be if you've made it up using 100 millicuries and followed all the instructions. That does not mean to imply that that's the only way that mag-3 can be assumed to be stable at six hours or that mag-3 won't be stable at 12 hours.

Now, there's an added issue here, and let me just get it out on the table and say it. Let's talk about how stability requirements find their way into package labels. Here's what happens: Drug manufacturer X is investigating a drug in its preliminary and then, finally, in its phase-1, -2, and -3 stages. It sets up a series of experiments by which drug stability is looked at and the use of the drug in clinical practice is looked at through a range of circumstances. Typically, they might, say, extend the loading of the vial in stability studies up to 500 millicuries of technetium and stability studies carried out to 12 hours, or 24 hours. Now, we're working in an environment that tells us fundamentally that the governing time of expiration of any technetium radiopharmaceutical is going to be the expiration of the generator elute, which is taken to be, arbitrarily, 12 hours at the moment, and that's based on some notions about what the bacteriological

stability of a vial that is multiply punctured in which there is no stabilizer, there is no antibacterial agent, benzoic acid or something similar. The reason those things are not in there is that they tend to be oxidants and they would mess up the preparation of reduced radiopharmaceuticals.

So we've got this 12-hour number that we begin to work with as a starting point, which, many of us know, for certain radiopharmaceuticals, is actually not rational, but fine; we do it anyway. We've got that 12-hour number. Now the manufacturer says, Okay, I can go 500 millicuries; I can go 12 hours with ease; but let's just be on the same side, and let's say 150 millicuries and six hours, because FDA will not begin to argue with me about the adequacy of my data if I withdraw from my 500 and 12-hour documentation to 150 and 6 hours. And in the process, guess what I've accomplished? I've ensured that vial sales are increased by a factor of three, because I've got the NRC to help me force people to load the vials with only 150 millicuries.

[Laughter.]

DR. SIEGEL: Now, that's not ALARA, and I can tell you that I've had discussions with manufacturers where they have admitted to me that that's exactly the way they wrote the label. FDA doesn't say, You need to put in the label that you really can add 500 millicuries and take it out to

12 hours. FDA doesn't encourage people to claim things that are broader; they decide whether the claim that has been made is justified by the evidence. If it's not, they make the manufacturer withdraw from the claim or contract to a point that they believe is justified; but they don't encourage manufacturers to extend the claim, as a general rule.

It's in manufacturers' interest to game the system that way, and you're helping them game the system, directly or indirectly, and, in the process, helping to run up the cost of medical care, indirectly or directly.

I as a physician would do the following: If I were in something other than an academic institution, my approach would be a little different, but not too different. As a physician, I would sit down, and I would go to my radiopharmacist and say, You know, I don't understand why every day we're using mag-3, and it gets to be 3 o'clock in the afternoon and we have two more requests for renal scans, and we've got to make up another vial of mag-3, when we still have 80 millicuries left in the vial, six hours post-preparation. What percentage mag-3 have we still got now? So they run the QC for me at six hours, and they say, It's still 98 percent. I say, Let's use it, and let's keep a record for the next six months of exactly what happens when we tape that vial at six hours and do the QC again, and

see where we are.

So I start gathering data, at six hours, seven hours, eight hours, maybe nine hours, because that's sort of the end of the working day, and the vial's getting empty at that point. I look at the data and I say, We've got pretty good evidence that, when we go out to eight hours, we never have even a whit of a problem of that with mag-3 used under these conditions, and I say, I'm going to change our procedure and say, Mag-3 expires at eight hours or the expiration of the generator elute, whichever comes sooner, in case I made it up later, and that's now codified in my laboratory.

If I'm clever, I also do the following: I write that down in a paper in the Journal of Nuclear Medicine with the stability studies and make it available to the rest of the world. If I'm politically active, I get to Mallinckrodt, Inc., and I say, Listen, I've got this data, and I'll be you've got this data, too; why don't you change the package label and make it so everybody knows that this is the right way to use this product and that it doesn't have to be chopped off at six hours. For the practitioner who didn't gather all the data himself, at least my publishing it in the Journal of Nuclear Medicine makes the data part of the public record, if you will, and can show that there's reason to believe that it's good practice.

That's the way it happens, I think. Do you want to amplify on that, Bill?

CAPTAIN BRINER: I couldn't have said it as well, Barry. That's the way it happens in our shop, too.

DR. SIEGEL: Carol? And then Mark.

DR. MARCUS: I understand that FDA has a constraint when it talks about activity of technetium, based on the fact that the directions have to hold through the entire useful life of the generator, which is two weeks. If you never milk your generator for two weeks, and then, on the very last day, when it's to expire, you milk it for the first time, you wash down an enormous amount of tech-99, which all the tech-99m has decayed into, which is going to take up a lot of spots on the ligand you're trying to label it to.

Now, a nuclear pharmacist like Captain Brian or Barry Siegel, they're not going to buy a generator or leave it there for two weeks; they've milked it at 24 hours, 8 hours, 6 hours, 3 hours, even 1 hour before, so they know that the number of atoms of technetium is such that they are not going to overwhelm the ligand in the vial. The 150 millicuries may be a limit if you milk it at the end of two weeks, and FDA has no choice of that, but your professional knowledge gives you the choice of that.

That's a thing that pharmacists and physicians

know, and unfortunately has been a terrible misunderstanding, I think, which scientifically ought to be understood by everyone.

DR. SIEGEL: Mark?

DR. ROTMAN: The issue of expiration times I think needs to be addressed from a point that shows some of the ridiculousness of it. If you make your bone agent up at 7:00 in the morning, it's supposed to be bad in six hours; that makes it 1:00 in the afternoon. If you make it at 7:05, does that mean it goes bad at 1:05 exactly? At 1:06 it's no good; at 1:04 it's all right? If you draw up the dose at 1:04 and it expires at 1:05, but the patient it not injected until 1:15, does that mean that the stuff is bad? The impact of this expiration time has gotten so ridiculous * t our clinical radiopharmacist actually writes down to the minute when he injects the technetium into the kit and makes it, so that, when he writes his expiration dates on the labels, they might say -- we use military time -- 1326 or 1327 or 1314 that day. I can't tell you how many times we've had an emergency bone come in at 1:20, and I look at that bottle, and, Well, it went bad at 1317; I'm sorry; three minutes ago it expired, and we have to throw it out.

You have to understand that the expiration times are guidelines, not gospel. It's like when you get a prescription filled at a regular pharmacy that says, Do not

use after a certain date. If it says February of '92, does that mean on March 1 of 1992 the stuff is poisonous, and on February 27 it's still good to use? You see, expiration times are a guideline, something to give you an idea of its useful life. They're not cut in stone. Saying six hours doesn't mean that at exactly six hours this stuff flips over in the bottle and you see its belly and all four legs sticking up.

[Laughter.]

CAPTAIN BRINER: I think what Mark said is totally true. The expiration times reflect a steadily degrading process that starts from the moment you start timing, and it ends after the time that somebody estimates that this is where you ought to stop using that drug. It does not start and stop on a dime, as he quite correctly said.

DR. SIEGEL: I would add, though, that I think that practitioners -- pharmacists or physicians -- who codify a deviation from manufacturer's instructions have an obligation to have a scientific basis for so doing. We have a responsibility to our patients to be certain that the products we're using will give us good scientific results with doses that are ALARA, and all that other wonderful stuff, and won't cause nasty reactions -- which very few of our things do.

When I go beyond the bounds of a package label for

anything other than an occasional emergency situation, I do so based on the knowledge that there is either good scientific data in the literature that support the practice or that I have documented so doing in my own hands. I personally would think it would be not terribly responsible if someone just said, Gee, you know, I'll bet you we can do more bone scans if we just add a curie to the vial; let's start doing it tomorrow. The answer will be you can do more bone scans, except they'll look like thyroid scans in some instances. You shouldn't do it until you've got the data to prove that it's sensible.

But the point is that the notion of professional responsibility carries with it the concept that that's the way you do things. Now, are there bad apples in the world? Of course there are, and we know there are, but I encourage you, as I have repetitively, to think about regulations in terms of the professional behavior you expect for professionals, and that professional behavior is motivated by the belief of wanting to do the right thing and having the scientific basis for so doing.

Naomi had a comment.

DR. ALAZRAKI: I just wanted to make two points. First, you're spending a lot of time talking again about the six-hour rule, and we still don't really know whether that's something that the NRC believes it should be authorized to

comment on or not.

Number two, in terms --

DR. SIEGEL: We're not making decisions; we're providing guidance right now.

DR. ALAZRAKI: Guidance. I understand.

Number two, in terms of the discussion about radiopharmacists, radiochemists, there is really a sparsity in terms of the numbers of these people in the field. The Society of Nuclear Medicine has about 12,000 active members. The Radiopharmaceutical Science Council has less than 200 members; that includes radiopharmacists and radiochemists. In terms of the numbers who are out there in the field, actually practicing radiopharmacy, not as part of, let's say, commercial or manufacturing groups, is really very, very few relative to the number of practices out there.

That's why, I think, in generally, historically, technologists have been trained in terms of compounding and radiopharmaceutical and quality control of radiopharmaceuticals, and in most practices around the country it's the technologist working under the supervision of the physician in terms of performing that practice, and the number of other qualified individuals are just not there to support anything else. And that has worked fairly well, in terms of the performance history of the safety of radiopharmaceuticals administered in this country.

I just wanted to make that comment, for the NRC to realize what we're talking about in terms of numbers of trained people.

DR. SIEGEL: Thank you.

MR. CAMPER: Okay. The one final point that I have is, as we did earlier with some of the language submitted in the petition, I would just like to get any input from the committee on the language.

Under the category of statements of consideration in the petition, they said, "To allow the practice of institutional nuclear pharmacy, the section that describes permissible sources of radiopharmaceuticals must be expanded." They recommended text for insertion in 35.49, which says the following: "Byproduct material in radiopharmaceuticals compounded by or under the supervision of a state-licensed nuclear pharmacist or nuclear medicine physician, if such radiopharmaceuticals are manufactured, prepared, propagated, compounded, or processed under an exempt category of section 510(g) of the federal Food, Drug, and Cosmetic Act."

My question is, would any committee members care to comment on that language, to add to it, delete from it?

DR. MARCUS: Was that the whole sentence?

MR. CAMPER: Yes. And this is for institutional nuclear pharmacy.

DR. SIEGEL: One question that might come up is whether the language specifying nuclear pharmacists or nuclear medicine physician should really be the pharmacy authorized user, in the concept we talked about a moment ago, before lunch, and physician authorized user, because, again for restraint-of-trade type considerations, I would not want to imply that nuclear medicine physicians, meaning people certified by the ABNM, are the only physicians who would have the training and experience to make these judgements, nor would I necessarily imply that a pharmacist who was not a board-certified nuclear pharmacist but who had met the proposed concept of new criteria in subpart (j) wouldn't be able to do that.

DR. MARCUS: Barry's interpretation was the intent of the petition. That's what we meant.

DR. SIEGEL: The other issue is, just from a regulatory-language point of view -- and this is a lawyer job and not an advisory committee job -- talking about exempt categories in the 510(g) as such, as opposed to trying to get better definition of what those exemptions really are, would be a way of clarifying it.

One thing that I know was mentioned clearly in the petition that we really haven't talked about today is reference to the nuclear pharmacy guidelines, because the nuclear pharmacy guidelines make it reasonably clear that

most of the kinds of activities that we have been talking about are things that the FDA, when those guidelines were published a number of years ago, thought were within the purview of the practice of pharmacy and did not by default require that the pharmacy had to register as a drug manufacturer and thereby be subject to all the inspection provisions that go with that, and did not by default require either a new drug application or IND, although it was conceived that there were certain circumstances under which the FDA might make a determination that such would be required. Those situations still remain to be defined, in many instances, but the nuclear pharmacy guidelines really make it pretty clear, and the FDA bought off on it, about what it is that pharmacists do in the course of their activities, and that extends all the way through some compounding from raw materials of things that ultimately become reagent kits.

When you do that, you've got a responsibility. You've got a professional responsibility to make good stuff, not garbage.

MR. CAMPER: Mr. Cunningham, Dr. Glenn, any questions?

MR. CUNNINGHAM: I don't believe so.

DR. SIEGEL: What's next?

MR. CAMPER: Radio-labeled biologics.

DR. SIEGEL: Oh, biologics. Okay.

MR. CAMPER: Okay.

The last broad category, then, is, should medical licensees be allowed to use any radio-labeled biologic for which a PLA has been approved by the FDA? First I would like to point out that there is a document now available -- we've entitled it NUREG CR 444, "Radiation Safety Issues Related to Radio-Labeled Antibodies." We think it's a worthwhile text. We've gotten some good feedback on it. If you're not aware of it, you might want to take a look at it. It does deal with the subject fairly well, we think.

DR. SIEGEL: Was that made available to all matters of the advisory committee?

DR. MARCUS: No. I would like --

MR. CAMPER: We can certainly do that.

DR. SIEGEL: A couple of us have copies of it already.

MR. CUNNINGHAM: I think we can get everyone a copy.

DR. SIEGEL: Good.

DR. MARCUS: Good.

MR. CAMPER: Basically, I think, in looking at this particular issue, we can narrow it down to three questions, or three issues. Primarily the concern with the biologics is that the technical aspects of using some of

these materials are quite different than the normal radiopharmaceuticals typically used in the practice of nuclear medicine. Some of them, as we've talked about, are higher-energy beta emitters; some of them are alpha emitters, although that's probably not our particular problem; some of them involved or might involve longer infusion periods; some of them could be multiple curies in nature.

What I would do is characterize our three areas of concern really as follows: how to place the biologics in part 35; the second, really, is a broad issue of the radiations safety requirements associated with these materials; and by far, I think, our greatest concern is the radiation safety requirements associated with these materials and how we might go about addressing them. To some degree, although we intend to really deal with this particular question as we talk with FDA, the process and the attention paid by FDA in looking at PLAs as it relates to any radiation-safety related kinds of things, or dosimetry, and this type of thing.

So really what we're looking for it any general guidelines or input the committee members might have, primarily on the placement of the biologics in part 35 -- for example, I mean by that, should they be in a separate category? Our inclination is that they would not be, but

should they be? And then the implications as it relates to radiation safety and suggestions for how we might approach that particular problem area.

DR. SIEGEL: Dick?

MR. CUNNINGHAM: Before the committee starts discussing this, I would like to emphasize something that Larry just said, because I think we in the staff are a little bit responsible for mixing two separable things. One is, where does a PLA fit in part 35, insofar as it applies to routine uses of radioisotopes in drugs? Are there any special training requirements on the part of physicians for administering these drugs, not radiation safety, mind you, as it applies to the laboratory, and any other kinds of special considerations? Can they be included, PLAs, along with INDs and NDAs, in the way we currently have NDAs and INDs? Beyond that, there are health physics considerations, just laboratory, radiation safety. We have heard all kinds of stories. We don't know how it's going to finally shake down; it depends on who you talk to. We've heard about alpha emitters, labeling these things in laboratories, maybe community hospitals that don't have a lot of experience with handling iodine in non-encapsulated form, and so forth, down to labeling using technetium generators in a way that isn't much different from labeled pharmaceuticals.

I think the most important contribution this

committee can make, as a committee, is with the former issue. To the extent later on, either as a committee or as individuals who have worked with this, on the health physics part of it.

Thank you.

DR. SIEGEL: Okay.

Let me express an opinion and then see how the rest of you react to it. My opinion is that the radio-labeled biologics, either prepared and distributed as radio-labeled or prepared and labeled in kit form, that are likely to hit the street anytime soon will be indistinguishable for all practical purposes from the radio-labeled drugs that are currently in distribution, and they will be drugs that are going to be used for diagnosis. Available evidence suggests that the safety considerations in their use as drugs, despite the general grave concern that there would be a high frequency of reactions to mouse-derived products, has proven not to be a serious problem in their general use, even for individuals who have had more than one exposure to those products. There are occasional problems, but they are relatively few. I think you can be reasonable sure that FDA will address those problems in any labeling that comes with those drugs.

You are going to have an opportunity to watch, in all likelihood, and see the experience without having to

worry about it, because the first product that probably will be approved is one that will be labeled with indium-111. It will be non-byproduct material, and you can kind of sit back and see what happens for a while before you have to fret.

But I would recommend that diagnostic biologics basically be brought into the umbrella of what you now call drugs in part 35. They're not going to be any different.

It is my sense, as well -- that this is a bit more in the crystal ball -- that the first classes of therapeutic biologics that hit the street aren't going to be a whole lot different, in terms of either their use or preparation or radiation safety considerations from what we've currently got rolling for giving 200-millicurie doses of I-131 for patients with thyroid cancer. It's going to be in the same ball park.

I think we've got a long way to go before you're going to have to worry about any astatine-labeled radiopharmaceuticals out there emitting beta particles. There's a lot of basic radiobiology work that yet needs to be done, an incredible amount of work that would need to be done to satisfy FDA, before those things would get to the street.

I also think that FDA is going to protect you on your other issue. I find it very difficult to believe that kits that involve cooking up curie-quantities of I-131 with

protein in hospital fume hoods, with not even a formal radiopharmacy, are going to happen. There's precedent for this sort of thing. Certain drugs have been licensed by FDA with the understanding that their preparation occurs only under certain conditions.

DR. MARCUS: Chemotherapy.

DR. SIEGEL: Chemotherapeutic drugs, for example, some of them, fit that kind of character.

Although some of these drugs might have to be made regionally and couldn't all come out of a plant in St. Louis or a plant in North Billerica or wherever, my sense is that arrangements whereby such things were only prepared in regional radiopharmacies and simply could not be purchased by a community hospital is what would happen, and that FDA would insist on that because the necessity of insuring stability of the product was so high.

But that's down the road yet. There is not yet -- and maybe Mark would disagree with me -- a therapeutic, radio-labeled antibody that's ready to be commercially marketed for general use.

Carol?

DR. MARCUS: Not only that, what I see really down the line is that we won't be using mouse monoclonals. I really think that the kind of work that's being done at Caltech and all, defining the particular part of the

antibody molecule that's responsible for targetting will result one day in someone dialing into his PC basically a robotic system that will synthesize de novo a peptide and will not be a biological anymore. It will be probably under drugs again. Worrying about when it is a biological and when it is a drug is not, probably, the best way for you to spend your time. I mean, you could kill yourself on all these regulations, and we turn around and synthesize one of them, and it's not a biological anymore, so don't worry about that.

Remember, in the case of the chemotherapy agents, even if FDA wasn't noticing, OSHA was, and OSHA didn't like people messing with chemotherapy agents except under very specific, safe circumstances. I wouldn't worry very much about the precedent of limiting availability of these drugs. It has been done before.

And certainly I wouldn't worry about whether you call something a drug or a biological. We are, of course, using biologicals now and have used them for many, many years -- serum albumen and compounds derived from that, microcolloids, macrocolloids, macroaggregated albumen. Fibrinogen was labeled. That really is a biological. That happened to go through drugs. We use red cells, white cells, and platelets from patients, and that doesn't go through anybody. We use stuff from the blood blank, and

that does not have an IND, an NDA, or a PLA.

I think, if you worry too much about these boxes, you end up with a regulation that is not as broad as you really need it to be, so I wouldn't worry about any of those things, just expand the regs to include anything that has approval or acceptance by FDA, without all the little details, and we'll be okay.

That's really what the petition said: Don't restrict yourself, and then we don't leave out something by accident.

MR. CAMPER: Well, we seem to be hearing across the board from part 35 licensees that use of approved PLAs would be satisfactory and acceptable and quite reasonable.

One other question that Mr. Cunningham alluded to, and that was this question of training. I would ask the question broadly in the following sense: Is there a need for our agency to be concerned about training, either in terms of basic training in our minimal training requirements or continuing training requirements, or interdisciplinary training requirements, particularly as it relates to, say, therapy agents?

DR. MARCUS: You mean with biologicals?

MR. CAMPER: With the biologics, yes.

DR. MARCUS: Nothing inherent in biologicals. Every physician knows how to treat allergic reactions.

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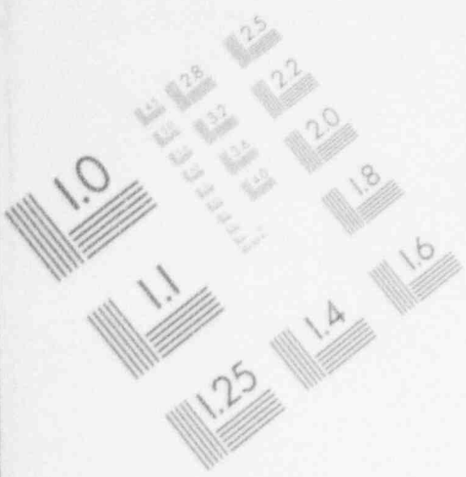

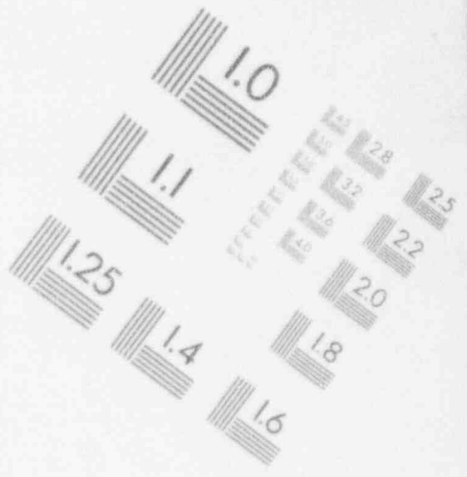

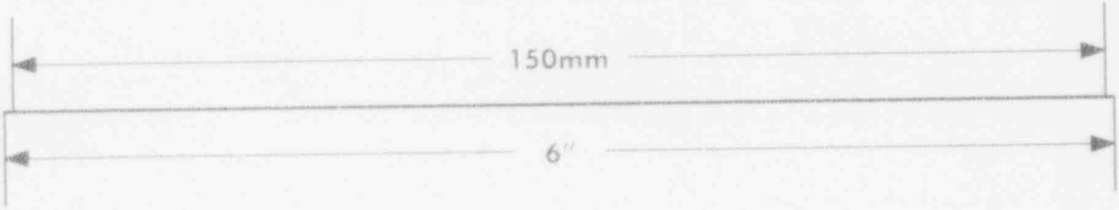

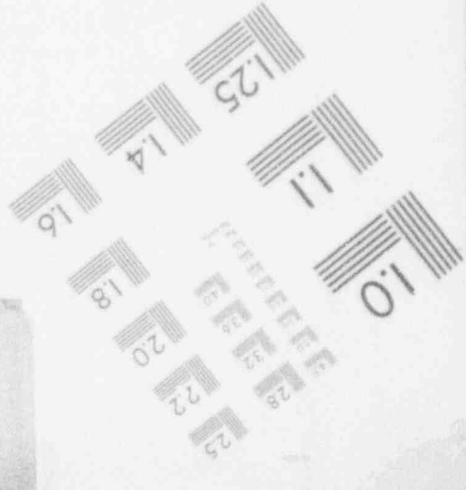

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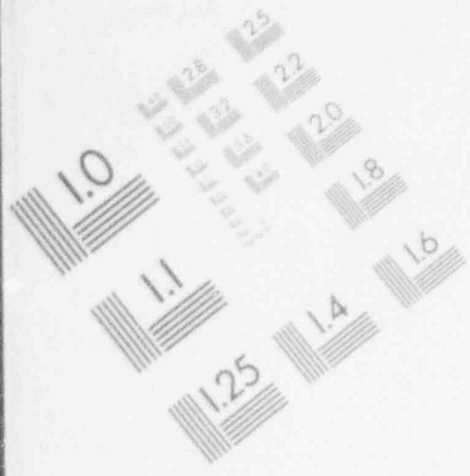

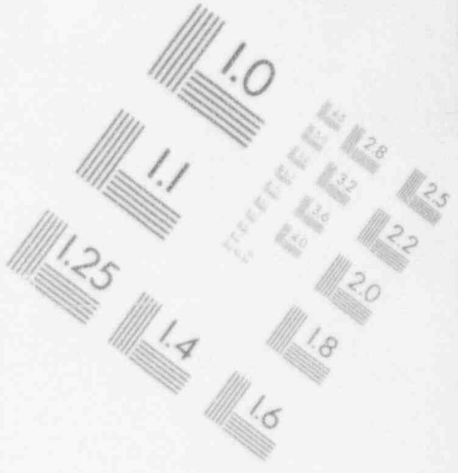

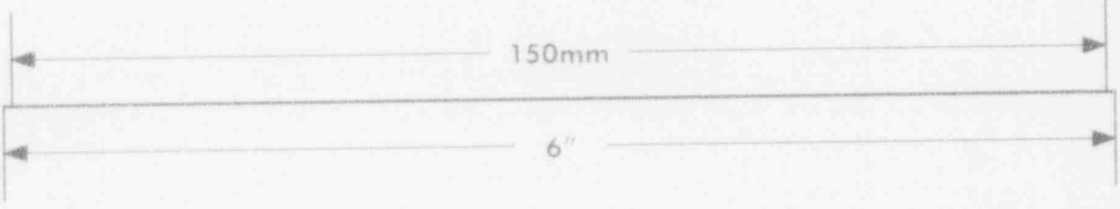

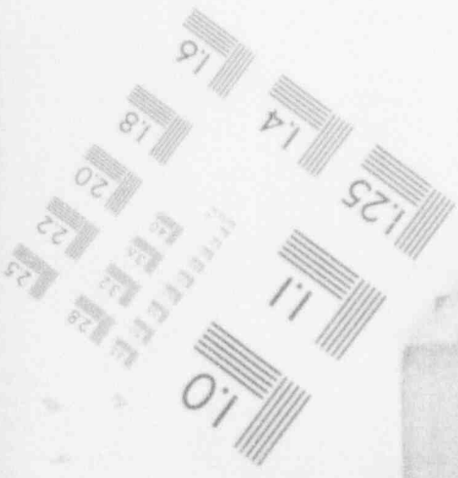

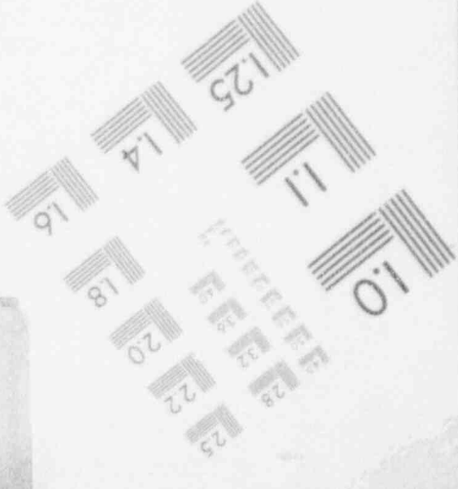

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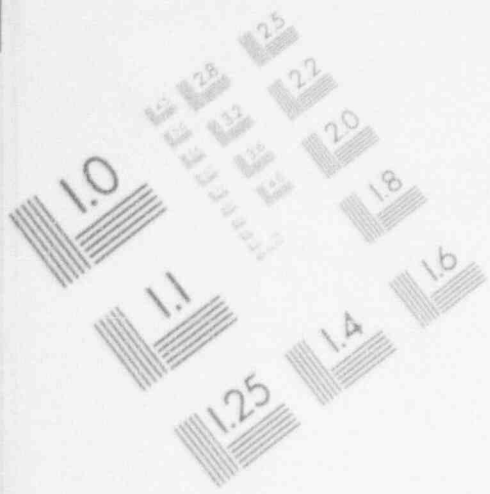

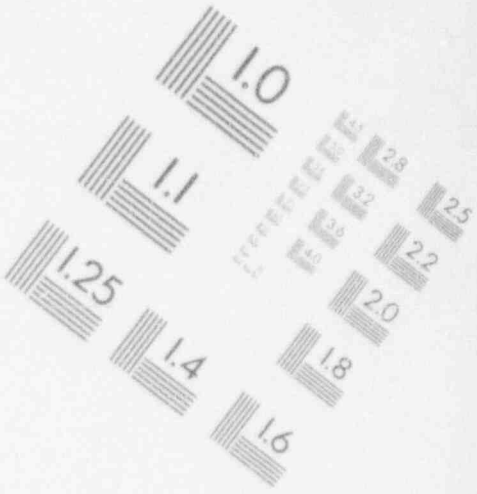

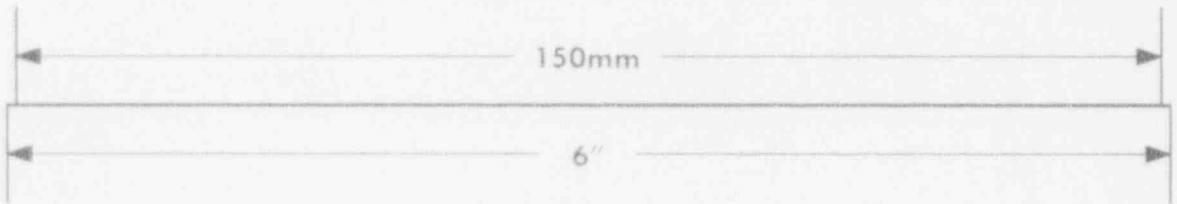

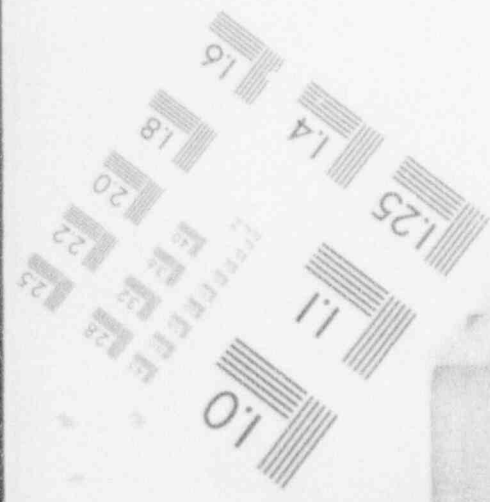

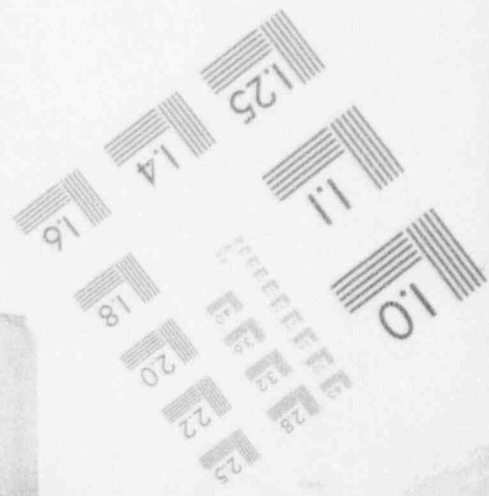

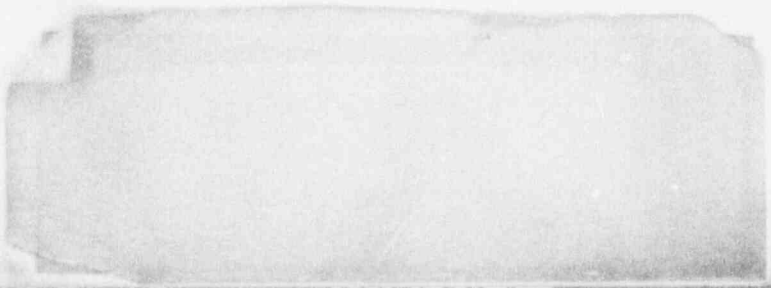

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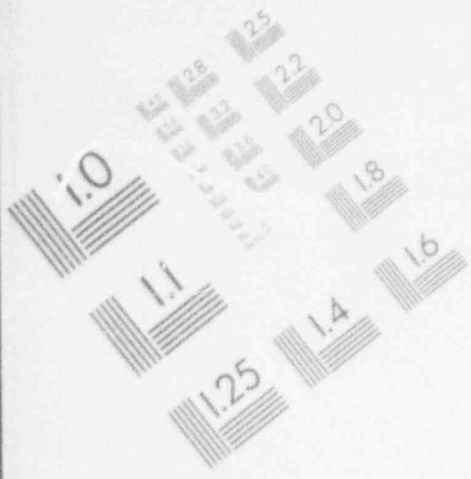

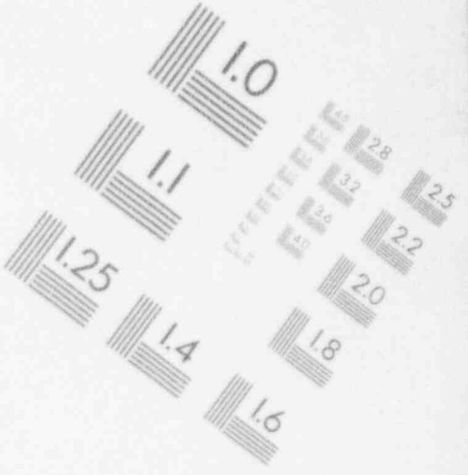

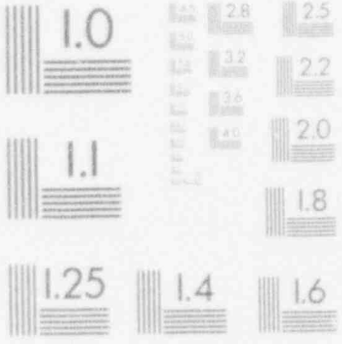

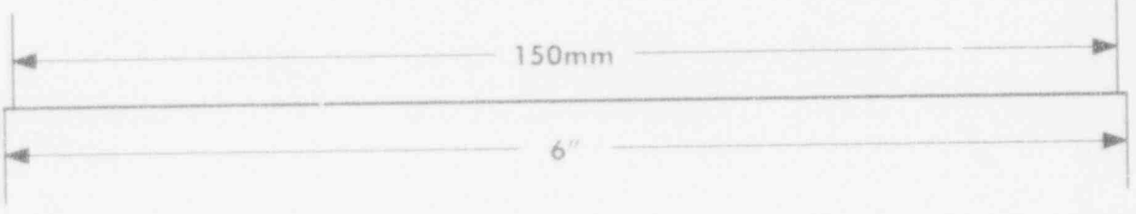

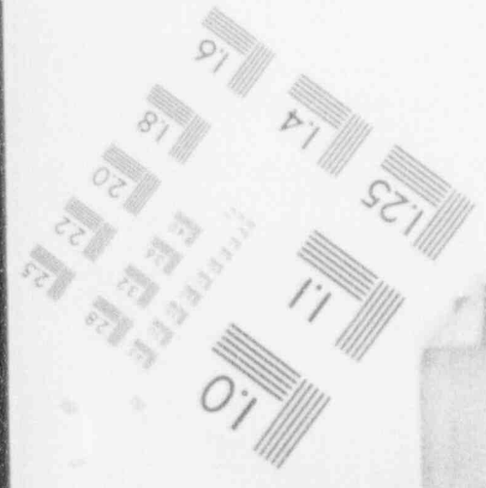

As Mark said, complex things mean you have to have more training, but I don't do neurosurgery because I haven't had the training, and a guy who has very, very little experience in radiopharmacy doesn't go out and start labeling complex antibodies or start making petrobes, because professionally he knows that he cannot yet be responsible for the product, so he just doesn't do it.

I think what happens is that it grows. A pharmacist with some amount of training suddenly gets asked, Can you do X. I have asked a pharmacist, Would you make me sodium iodide IV? The first guy I asked said, No, because I never have, and I'm not really sure how to do it, but why don't you ask this other nuclear pharmacist; I think she has. So I just kept going up until I found a professional who was confident in ability.

If suddenly everybody was asking the pharmacist to make something new, you would find that nuclear pharmacists would get together and find out exactly how to do it. When they were sure they could do it, then they would offer the service, and that's what happens with all of us. New drugs come out, new procedures come out for nuclear medicine physicians for which they were not trained in their original training, but they obtained training of a sort so that they can offer them.

I didn't learn SPECT when I was a resident. I

didn't learn to use many of these news drugs when I was a resident, but there are ways a professional continues their education so that they are then able to do it. I have used many drugs for the very first time without ever having been supervised by anyone in that use, but I make sure that I understand what I'm doing before I do it.

DR. SIEGEL: I might just back off from that position a little bit, to say that it's hard to speculate about those safety issues with the use of a drug that we don't know about yet. To categorically say that anybody who is currently approved as an authorized user for therapeutic I-131 for cancer therapy will almost certainly have all the skills necessary to do therapy with a radio-labeled antibody that hasn't been conceived yet -- it may be risky, but you don't lose much by keeping your options open, because right now there's no burning issue. If one finds that there are in fact important safety issues that need to be addressed, you have an option to deal with that on byproduct material, biologics or therapeutics, before they ever hit the street, because that product is going to need to have a license from you before it hits the street. If you're concerned about something, you have an opportunity to interdigitate yourselves and to get advice from us about what needs to be done before it is a problem for you.

I think, as we would conceive the use of the drugs

in their current concept, and based on what has been done right now, people who can give I-131 for cancer therapy have the skills that they need to give I-131-labeled antibodies. But I'm sure that there are going to be some exceptions to that rule in the future, but you have a way of dealing with that on a case-by-case basis, rather than putting in place some training and experience criteria now that will prove to be inadequate when the first one actually occurs.

Mark, you had a comment you wanted to make?

DR. ROTMAN: Back again.

To go backwards just a little bit, an indium-111-labeled antibody that was shake and bake, if that was available today, that would be clearly diagnostic use, but that same antibody could very easily be labeled with a therapeutic isotope -- yttrium-90, for example -- with no changes at all in the methodology. If you were to look at millicuries injected -- 5 millicuries of indium, 5 millicuries of yttrium-90 -- 5 millicuries of yttrium-90 doesn't seem like it would be therapeutic, yet the dosimetry to the target would make it therapeutic. You're going to have to look a little bit at the intent and what it's going to be labeled with.

To bolster what Carol said, in 1983, when we started out on our program to use radio-labeled antibodies for therapy, nobody had really done it, and we didn't have

any idea of what we were going to do, but we just sat down with our radiation safety branch and looked at the amount of lead and the amount of ventilation and the sort of facilities, and we built it and started doing it. We fine-tuned it as we went along, and now I radio-label hundreds of millicuries of antibody. I do two or three reactions simultaneous, I'm so comfortable with it. We used HPLCs for purification. Things two or three years ago I wouldn't have dreamed were even possible we're doing daily now. We're in the process of building a robot to do the yttrium labeling for me, so I don't get blasted. A year ago I didn't even know that a robot could do that kind of thing, so for us today to even think about writing a regulation that's going to apply to something we don't know about in the future is really kind of off the wall.

You just have to trust that, with the radiation safety guidelines, the possibility of exposing yourself and trying to minimize that and protect your physician and your technologist and maximize the effect to the patient, your professionals are going to do the right thing. The technology is growing by leaps and bounds, and I think that, by the time you get even a formulative regulation written, it will have changed again, anyway.

You have to allow things to evolve. At a certain point they'll be state-of-the-art, and then you can look at

them and say, Well, maybe we need to address this issue, but right now you just need to be aware that there will be an issue.

MR. CAMPER: Sort of a crystal-ball question, at best: In the foreseeable future, are there clinicians that are not nuclear-medicine types that may become involved in the use of radio-labeled biologics? If so --

DR. MARCUS: With two weeks' training? Yes.

MR. CAMPER: Any feel for what they might be at this point in time?

DR. SIEGEL: Medical oncologists.

There is also a fair likelihood that radiation oncologists will have a moderate degree of involvement in this. The growing turf battle between radiation oncologists and nuclear medicine physicians and medical oncologists -- I mean, I think this committee has pointed out in the past that there seems some dichotomy between the 200 hours of basic science training and the six months training to learn how to read bone scans and the two weeks of training for therapy and the relatively limited amount of experience for therapy.

It's hard to know where to strike exactly the balance, given the amount of training and the number of cases that most people will be able to see during the course of a residency training program. That's in part what those

numbers are predicated on.

Very, very busy training programs that train nuclear medicine residents may do 25, 30 thyroid cancer therapies a year. Smaller programs may do only a few a year, and if radiology residents are going to learn that skill and have to pick it up during six months in the course of four years, that's why you sort of get down to the numbers at three and the numbers at ten for hyperthyroidism.

But if you push that to drugs that are more and more complicated to use, looking at the training and experience criteria, once you see what you're dealing with, may be appropriate. You're going to have ample warning. I mean, you'll know that something is under review at FDA, and there will be enough out in the literature about conditions of use before you have to react to it. You won't have to react the day you get an applications from a manufacturer for a license to distribute a radio-labeled biologic for therapy.

Mel?

DR. GRIEM: In pediatric radiotherapy, for instance, my daughter, who is in that field, went to another hospital to get the training and made arrangements to be there for four months to pick up that particular discipline. The hospital where she was at did not see enough pediatric cases, so she went there. In another situation, she went

over for four months to the Mass. General Hospital to pick up a specific thing that she wanted in the treatment of cordomas next to the brain stem. The people who do it will be really quite specialized, and I don't see this as being an immediate problem.

I think, when the agents are worked out, there will be people will go there and pick up the discipline. I don't see a nuclear medicine person taking on something that will be very specific from the standpoint of formulating, say, a receptor-directed drug or something membrane-directed, or something like that, which may be the way of the future.

DR. HERRERA: Barry?

DR. SIEGEL: yes.

DR. HERRERA: If you put together some of the things that Carol mentioned in terms of genetic engineering, so that you can synthesize peptides that are specific for this receptor, and put that together with the issue of labeling those so that they can have a therapeutic effect, if you're going to the crystal ball case, you're going to have all kinds of therapies that do not exist at the present time for all kinds of things. It's impossible to draft regulations at this point for that.

The second point I wanted to make: The fact is that physicians of all types are constantly, constantly in

continuing medical education, learning new techniques that they then, once they feel confident, apply to their practices. That's how arthroscopic surgery has spread through the country; that's how all of these new things are spread. People go and take courses, and they keep on doing this until they gain the experience and the ability to be able to perform these new techniques.

DR. SIEGEL: To summarize this notion about therapeutic biologics, I think it's safe to say that we would recommend that diagnostic biologics basically be treated exactly as are drugs currently, but that you needn't burn any bridges with respect to therapeutic biologics until you have to face the issue with one. You didn't have rules with respect to afterloaded brachytherapy 20 years ago, and you had to come up with mechanisms and regulatory guides and rules that dealt with afterloaded brachytherapy, so that, as you well know, the rules are not meant to be static and unchanging; they're meant to accommodate the needs.

If it turns out that it seems clear that a radio-labeled biologic for therapy requires an extraordinary level of training and experience to use it safely -- which will become evident from what's in the literature -- that requires safety set-ups that are not likely to be found in most community hospitals, you are in a position to deal with those just as you would some new brachytherapy device that

comes along, and being much more specific than you are with the broad class of drugs.

You're already specific for types of therapy now. You discriminate therapy for hyperthyroidism from other types of therapy because you recognize the difference and the fact that one rule didn't work. Similarly, it may be that you're going to need a lot of rules someday to deal with multiple different types of therapeutic biologics; there's nothing intrinsically wrong with that, as long as those rules are sensible, related to the hazards.

Mark?

DR. ROTMAN: I want to reinforce what Dr. Siegel just said. At NIH, if you're going to give 8 millicuries of radioiodine for a Graves' disease patient, that's considered a therapy, and we get a full-alarm response from our radiation safety branch. We get papered rooms and all kinds of monitors, and we get forms to fill out. It's unbelievable.

If I give a 15-millicurie dose of yttrium-90 antibody, which is very therapeutic in what we're doing, they don't even what to know about it. They don't respond; they don't paper the rooms; they're not even involved at all, because to them yttrium is not dangerous. It's not a naturally occurring biologic element that's going to localize in any one particular gland. It's 99-and-such

percent bound to the antibody, which is not excreted in any way from the patient. They don't really want to know.

If it's I-131, they'll get involved, but just about everything else they don't care about, and so it's obvious that it's already happening, that some places are discriminating against what is considered actionable and what isn't in response to a therapy.

You may get a whole class of radio-labeled antibodies that are considered therapeutic that, from a lot of aspects, you don't have much to do with, except to ensure that the dosimetry is correct, perhaps, or that the assay of the dose and the dose calibrator is done in a prescribed manner.

I can tell you right now that what you have set up isn't going to be adequate.

DR. HERRERA: I'd like to address the issue of the community hospitals for a minute. Twenty years ago, chemotherapy was restricted to a very few centers in this country. Nowadays, practically every community hospital is doing chemotherapy and is doing it properly. Unless there is a significant change in the nature of this country and the way medicine is practiced, one thing that you can count on is that there is a horizontal spread of medical knowledge and talent in the count, and so it is that today already some community hospitals are getting involved in marrow

transplant, and on and on it goes.

Whatever the NIH is doing today, unless this country changes, and it's forbidden to spread, is going to be practiced in community hospitals within the next 10, 15 years, but at this point in time you cannot make those regulations.

DR. SIEGEL: Other comments?

[No response.]

DR. SIEGEL: Other questions?

MR. CAMPER: That's all.

DR. SIEGEL: Okay.

If so, I'd like to take a couple of minutes to readdress an issue that I think is important. At the meeting in January, and yesterday and again this morning, this committee expressed a philosophical viewpoint with respect to the quality assurance rule that I think warrants some clarification. I'm going to frame this, and then you all may choose to agree or disagree with me, as you see fit.

The nuclear medicine community, the radiotherapeutic community, I think has been opposed since day 1 to the misadministration rule when it first appeared, tried to block the misadministration rule in the revision of part 35, in the hopes that it could make it disappear at that point, and at advisory committee meeting after advisory committee meeting, when misadministrations have been

discussed, members of the medical community have made it clear that they see the rule as iniquitous, as requiring to expose themselves to malpractice risk unnecessarily. Moreover, as I pointed out at the last meeting, serving as the focus for the Nuclear Regulatory Commission's raison d'etre in terms of its medical activity, what can we do to make misadministrations appear to be zero, so that we don't look bad when we make our report to Congress?

We saw the development -- we meaning the medical community -- of the quality assurance rule as an error-prevention based on this search for zero misadministrations as the Holy Grail of nuclear regulation.

I think this committee, as well as others, have made it clear that a zero rate is unachievable in human activity, number 1; number 2, that quality assurance activities are already heavily built into activities of medical practices; and, number 3, that there is a great concern that rules written with good intent by the Nuclear Regulatory Commission end up limiting the ability of medical practitioners to do their jobs effectively, because they tie our hands behind our back in a way that was not intended, and yet prevent us from doing our job effectively.

I don't think there's anybody who denies that the quality-assurance concept -- and quality; forget quality assurance; let's talk about quality -- are motherhood

concepts that you cannot help but believe in. It's appropriate to believe in wanting to deliver quality medical care. It's appropriate to believe in wanting to practice medicine without mistakes, and particularly without serious mistakes.

Now, at the last meeting the committee put forward a motion that was initially rejected for purposes of discussion as much as for any other reason that said, We don't need a quality-assurance rule of any sort, and that motion did not carry at the last meeting. What did carry was the notion that diagnostic things should not be part of the quality-assurance rule, and we then spent a considerable period of time -- ten hours or so -- discussing the find points of the language, with the idea being that, if a quality management rule of some sort -- quality assurance rule of some sort were to go forward, these are the things that would make it consistent with medical practice as it is today, such that it would not be an overwhelming burden on people, would perhaps help them improve what they're doing -- perhaps, and that's a big perhaps -- but would not so burden them as to greatly limit their flexibility in the practice of medicine.

The staff responded to the ten hours of discussion with the ACMUI, along with the many, many days of discussion with the working groups, and generated a rule that I would

personally characterize as one that is certainly vastly improved from what we saw in January and, more importantly, contains within it concepts that most of us do not fundamentally disagree with, even though we may still disagree that the NRC should be telling us that we should do these things. Rather, most of us think that we should do those things because we know them to be right and are already doing them, and are troubled generically and overwhelmingly because of a philosophical framework that what we think is okay and probably can live with you telling us to do will end up not working for someone else whose practice circumstances we haven't fully considered, and therefore what sounds okay at this moment is going to end up shooting someone in the foot unintentionally, which is the risk that always runs with any kind of rulemaking.

I personally think that there is much that is good in the quality-assurance rule as it is written. I personally also think that there are procedures contained within that rule that most prudent nuclear medicine practitioners and most prudent radiations oncologists have either already adopted or would adopt if the reasons for so doing were made clear to them because of the ability of those procedures to make one's practice just a little bit more careful, a little bit safer, and reduce even further the very low likelihood of certain adverse events that

occasionally occur.

I think that what this committed voted to do last time and then again this time was to express its continuing belief that are philosophically opposed to the increasing interdigitation of the NRC into our daily decision-making process, even though it's the stated policy of the NRC to minimize those intrusions. We saw the quality-assurance rule at its inception a couple of years ago as a major intrusion. We saw the January, '90, version as still an intrusion, the January, '91, version as still an intrusion. Although the rule now contains things that -- Carol didn't like the word I used yesterday, but things that are livable -- the concept that you feel the need to make the rule is still an intrusion, even though we probably can live with much of it if we have to.

Now, members on the committee may disagree with my interpretation of our actions, but I think it's important that the staff be congratulated for the work that they have done in trying to make this rule better. For me to speak on behalf of the advisory committee, to thank the NRC for paying attention to us and for paying attention to our advice in terms of making the rule that you plan to send to the Commission one that is more reflective of what really goes on out there in the medical community.

People on the committee may react to my statement

if they choose.

CAPTAIN BRINER: I for one agree with you totally, Barry.

DR. HERRERA: I agree.

MS. McKEOWN: Me, too.

DR. MARCUS: I think we probably all agree. That was the basic point that we have been making all along.

I think the fears that you expressed as to how the rule might not apply to other people or not apply in certain circumstances even to people that have a good quality-assurance program, or could be subverted by some inspector who perhaps does not really understand what's going on, is a very, very real fear in all our minds.

The newest problem I have is that we are paying twice for a service: paying JCAHO to review our quality-assurance programs, and then being told to pay NRC to do the same thing. I don't think that we should have to pay twice. I think many physicians will feel that, and I think you are right, Barry, that all physicians feel that good quality is an essential part of what they have to do and that they try to do it very hard.

I think that NRC has made some improvements in the concept of misadministration reporting that are getting closer to what I think is appropriate. I would like to see some of these changes that are in the draft I wasn't suppose

to see incorporated for the time being. I still think it could be made even better, but certainly it is an improvement, because the original misadministration rule was extremely poor. I in my mind don't even associate the misadministration rule with the QA rule at all. The QA rule was in answer to the misadministration rule. The misadministration was not a part of it.

The problems I had with the concept of a QA rule were separate from what I have said before in this panel: that NRC deserves to know about certain occurrences, when they are serious and when they are going to be asked by the public what they are doing about it. I would love to help design a rule in which harm was reported to the NRC, appropriately. I don't see that that has anything particularly to do with how one designs a medical quality assurance program. In my mind they're separate.

DR. SIEGEL: Peter?

DR. ALMOND: Barry -- Dr. Siegel, I couldn't agree more with what you say. I think we ended up in January with the concept that, given that we were going to have a quality-assurance rule, could we, working with the staff, produce one that was as good as we thought it could be. I was very impressed at the St. Louis meeting with what they had produced. They really had listened to, I think, the discussions of January and tried very sincerely to put

that in.

I haven't seen the final version, Carol -- it didn't filter down to Louisville -- but at least what we left with you in St. Louis I think is substantially included. I think that they genuinely tried. Along with Dr. Siegel, I want to commend the staff for doing that. I've been on this committee a long time, and this is not the first time, but it's certainly an indication that they want to listen to the advice that give and put it into the rule. I appreciate that.

DR. SIEGEL: Good. Other comments?

MS. McKEOWN: I agree.

DR. SIEGEL: What?

MS. McKEOWN: I agree with you 100 percent.

DR. SIEGEL: All right. So there is concurrence with my comments.

Are there other matters of business to come before this advisory committee?

DR. MARCUS: There was just the one detail of whether you wanted to finish getting the answer to your question about differences in regulations in state pharmacy boards, what the National Association of Boards of Pharmacy does, how it represents pharmacy, model pharmacy acts. Do you still want to know or not?

MR. CAMPER: I think not at this time. I think

it's a good point. What we will do is, as we go through the process over the next couple of years, dealing with these issues, I think we should make it a point to contact those organizations and bring their input to bear.

DR. MARCUS: Okay.

There was an immediately effective rule in March which stated that all petitions had to be resolved within 12 months unless the EDO said otherwise. The EDO is allowing three years or three and a half years for this rule, or what?

MR. CAMPER: I don't think we're prepared to comment on that at this minute, but we will follow up.

DR. MARCUS: It says 12 months unless Taylor says otherwise, and I just wondered if he addressed this particular rule, because you're talking about November, '92, and then onward --

MR. CAMPER: The date that I mentioned, November of '92, is the date that went to the Commission. We have not heard anything to the contrary. I think all of us are shaking our heads that we're unaware of what you're referring to. I can assure you that we'll leave here and go find out.

DR. SIEGEL: Let's let this matter perhaps be resolved by further discussion between you and members of the staff.

With that having been done, and since it looks like we are no longer quorumed, since the people are on their way to the airport, I'd like to adjourn the meeting, and I'll let John make it official.

DR. GLENN: I'd like to thank the members of the committee, and especially the chairman, for your attendance and advice at this meeting, and I do now declare that the meeting is finished.

[Whereupon, at 2:45 p.m., the meeting was concluded.]

REPORTER'S CERTIFICATE

This is to certify that the attached proceedings before the United States Nuclear Regulatory Commission

in the matter of:

NAME OF PROCEEDING: Advisory Committee on the Medical Uses of Isotopes

DOCKET NUMBER:

PLACE OF PROCEEDING: Arlington, Virginia

were held as herein appears, and that this is the original transcript thereof for the file of the United States Nuclear Regulatory Commission taken by me and thereafter reduced to typewriting by me or under the direction of the court reporting company, and that the transcript is a true and accurate record of the foregoing proceedings.

Mark Handy

MARK HANDY
Official Reporter
Ann Riley & Associates, Ltd.

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202-429-5120
American College of Nuclear Physicians
The Society of Nuclear Medicine

TO: Interested Parties

FROM: Kristen D.W. Morris K. DWM

RE: Society of Nuclear Medicine Pharmacopeia Committee report

DATE: April 29, 1991

Please find enclosed a report from The Society of Nuclear Medicine Pharmacopeia Committee on A Study of Current Radiopharmaceutical Practices: Adverse Reaction Incidence and Deviation from Manufacturer Package Insert. This report has been sent to the attached list of individuals for consideration during the May 9 & 10 Nuclear Regulatory Commission Advisory Committee for the Medical Uses of Isotopes.

If you need any additional information, please feel free to contact me at the number stated above.

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April 12, 1991

Naomi Alazraki, M.D.
Co-Director, Division of Nuclear Medicine
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Dear Naomi:

Enclosed are data coming from a study initiated by the Society of Nuclear Medicine Pharmacopeia Committee with subsequent data acquisition by its Chairman. I believe the information contained in this brief report may be of assistance as we request relief from the NRC Interim Rule.

Sincerely,

Edward B. Silberstein, M.D.
Professor of Radiology and Medicine

Enclosure
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A STUDY OF CURRENT RADIOPHARMACEUTICAL PRACTICES: ADVERSE REACTION INCIDENCE AND DEVIATION FROM MANUFACTURER PACKAGE INSERT

EDWARD B. SILBERSTEIN, M.D.
CHAIRMAN, PHARMACOPEIA COMMITTEE
SOCIETY OF NUCLEAR MEDICINE

Introduction

The Pharamacopeia Committee of the Society of Nuclear Medicine (Table 1) has several important missions (Table 2) which have been implemented by its membership in the last few years. These have included a study of the prevalence and type of adverse reactions seen by participating institutions to radiopharmaceuticals as well as to non-radioactive drugs employed in Nuclear Medicine procedures.

In addition, it was felt to be important to establish the frequency with which there are deviations from the manufacturer's package insert and whether such deviations are associated with resultant adverse reactions.

Materials and Methods

Twenty-one reputable Divisions of Nuclear Medicine (Table 3) performing over 5,000 nuclear medicine imaging procedures per year agreed to participate in this study. Each Center designated an individual responsible for filling out a monthly questionnaire which provided the necessary information (Table 4). The definition of adverse reactions, (appearing in Table 4) was that arrived at by consensus of the Pharmacopeia Committee.

Results

From September 1, 1989 through December 31, 1990 these institutions had performed 220,903 separate radiopharmaceutical administrations which had resulted in six adverse reactions (Table 5). Two of these were anaphylactoid in nature while the others were mild dermatologic problems. Adverse reactions to dipyridamole are anticipated to occur in a significant percent of recipients and were not counted unless infarction, hospitalization or death resulted. A total of 15,540 non-radioactive drug doses were given with no adverse reactions. Unequivocal vasovagal responses, with lightheadedness at the time of injection, bradycardia and immediate resolution of symptons in the supine position, and several instances of a sensation of metallic taste following injection of ^{99m}Tc-sestamibi, lasting less than 30 seconds, were not included.

Table 6 lists the number of institutions (n=20) using any of 12 specific deviations from the package insert. No adverse reactions were reported by any of these institutions relating to these 12 unapproved uses of radiopharmaceuticals found in Table 6.

Discussion

This survey, which is an ongoing activity of the Pharmacopeia Committee of the Society of Nuclear Medicine, indicates the remarkably low prevalence of adverse reactions to radiopharmaceuticals of approximately 1 in 40,000 doses. This is consistent with the administration of microgram amounts of radiopharmaceuticals which one usually gives only once rather than repetitively. There were a significant number of institutions employing procedures which were not on the package insert with no adverse reaction response ever found. It should be added that each of these institutions had its own Investigational New Drug permit where necessary as well as approval of the Institutional Review Board for such procedures whenever materials were employed in a research setting.

TABLE 1

SOCIETY OF NUCLEAR MEDICINE
PHARMACOPEIA COMMITTEE

Neil M. Abel, M.S.
Rockville, Maryland

Capt. William H. Briner
Durham. North Carolina

Michael A. Davis, M.D., Ph.D.
Westwood, Massachusetts

Edward A. Deutsch, Ph.D.
St. Louis, Missouri

Donald R. Hamilton, MBA
Sykesville, Maryland

Linda C. Knight, Ph.D.
Philadelphia, Pennsylvania

Carol S. Marcus, Ph.D., M.D.
Torrance, California

John G. McAfee, M.D.
Washington, D.C.

John R. Scott, M.Sc.
Alberta, Canada

Edward B. Silberstein, M.D.
Cincinnati, Ohio

Gopal Subramanian, Ph.D.
Syracuse, New York

Dennis P. Swanson, R.Ph., M.S.
Pittsburgh, Pennsylvania

Wynn A. Volkert, Ph.D.
Columbus, Missouri

TABLE 2

MISSION STATEMENT: PHARMACOPEIA COMMITTEE

This Committee has as its mission:

1. to implement and monitor an Adverse Reaction Reporting System in conjunction with the U.S. Pharmacopeia, providing the results to the membership of the Society on a continuing basis;

2. to work closely with the U.S. Pharmacopeia on issues of drug standards and dissemination of drug information;

3. to provide expertise in advising and assisting the Society of Nuclear Medicine on governmental regulatory issues relating to drugs, biologicals, and drug-producing devices used in the practice of Nuclear Medicine;

4. to maintain liaison with the Radiopharmaceutical Committee of the U.S. Council of Energy Awareness and other groups relating to the radiopharmaceutical industry;

5. to exchange information with the American College of Nuclear Physicians Radiopharmaceutical Committee.

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TABLE 3

SOCIETY OF NUCLEAR MEDICINE
Institutions Performing Adverse Reaction Follow-Up

University of Alabama Hospital
Birmingham, Alabama

M.D. Anderson Cancer Center
Houston, Texas

Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Universeity of Cincinnati
Medical Center
Cincinnati Ohio

University Hospitals of Cleveland
Cleveland, Ohio

Cornell Medical Center
New York, New York

Dana-Farber Cancer Institute
Boston, Massachusetts

Duke University Medical Center
Durham, North Carolina

Cross Cancer Institute
Edmonton Radiopharmaceutical Centre
Edmonton, Alberta, Canada T6G 1Z2

Indiana University Medical Center
Indianapolis, Indiana

The University of Iowa
Iowa City, Iowa

University of Kentucky
Lexington, Kentucky

Mallinckrodt Institute of Radiolo
St. Louis, Missouri

Massachusetts General Hospital
Boston, MASS

Mayo Clinic
Rochester, Minnesota

Michael Reese Hospital and
Medical Center
Chicago, Illinois

State University of New York
(SUNY)
Stony Brook, New York

State University of New York
Syracuse, New York

Temple University
Philadelphia, Pennsylvania

The University of Utah
Salt Lake City, Utah

VA Medical Center
Bay Pines, Florida

TABLE 4

MONTHLY RADIOPHARMACEUTICAL AND ADVERSE REACTION REPORTING FORM SOCIETY OF NUCLEAR MEDICINE PHARMACOPEIA COMMITTEE

1. Institution _____ Month _____ Year _____

2. Total radiopharmaceutical doses for month (include IND, NDA, and all other radioactive drugs and biologics for diagnosis and therapy) _____

3. a. Total non-radioactive pharmaceutical doses for month in your Nuclear Medicine practice (include dipyridamole, captopril, glucagon, morphine, Lasix, TSH, TRH, Lugol's solution, ssKI, Cytomel, perchlorate, Diamox, lithium, pentagastrin, etc. _____

   b. Total stannous pyrophosphate doses per month _____

4. Adverse reactions to radiopharmaceuticals: Yes ____ No ____ Date _____ (See other side for definitions).

5. If yes, attach copy of USP Drug Product Problem Reporting Program form.

6. Total non-radioactive pharmaceutical reactions. Describe what happened and with what drug. (Include any gastrointestinal or cardiovascular side effects whether or not they require hospitalization. Do not include mild asymptomatic hypotension). _____

7. (Answer only if reactions are reported this month).

   Reported rating of suspected drug reactions (definitions below):

/ / Definite / / Probable / / Possible / / Doubtful

8. Person completing form _____ Date: _____
   (print)

DEFINITION OF ADVERSE DRUG REACTION:

Patient adverse drug reaction (ADR) is any response to a drug which is noxious and unintended, occurring at doses used in man for prophylaxis, diagnosis, therapy of disease, or for modification of physiological function.

Significant adverse drug reactions should be reported and include:

1. Untoward effects that are known effects of the drug, but have been reported infrequently or rarely.

2. Untoward effect that resulted in a complication or prolonged hospital stay.

3. Toxic reactions that occur in "therapeutic range" of monitored drug concentrations.

4. Allergic reactions.

5. Potentially serious, life-threatening or fatal reactions.

6. Any adverse reaction that resulted in a hospital admission.

7. Vasovagal response (hypotension, bradycardia)

(OVER)

TABLE 5

Adverse Reactions to Radiopharmaceuticals From 220,903 Administrations Sept. 1, 1989 to Dec. 31, 1990

RADIOPHARMACEUTICAL	REACTION	NUMBER OF CASES
Tc-99m DTPA	Erythematous rash	2
Tc-99m HDP	Erythematous rash	1
Tc-99m MDP	Nausea, rash	1
Tc-99m MDP	Tongue swelling, lightheadedness, responding to Benadryl	1
I-123-MIBG	Tachypnea, nausea, faintness, chest tightness, lightheadedness	1
TOTAL		6

TABLE 6

Deviations From Package Insert by
Twenty Broad License Divisions of Nuclear Medicine

	DEVIATION	NUMBER OF INSTITUTIONS DEVIATING
1.	Indium-labeled platelets	13
2.	Compounding radiochemical to produce a radiopharmaceutical (Xe, MIBG)	11
3.	Ignoring 6 hour rule	10
4.	Microcolloid for marrow, lymph node or leukocyte scan	8
5.	P-32 for treatment of thrombocytosis	7
5.	Eluant dilution when Tc-99m content might cause radiolysis	7
7.	Use Tc-99m greater than package insert allows	6
8.	Homologous WBC	5
9.	Parenteral iodide administration	4
10.	Ascorbic acid added to DPTA, MDP for stabilization.	2
10.	Tc-99m gelfoam imaging	2
12.	Indium added to "cold" kit of DTPA	1

In the institutions surveyed, the maximum number of "deviations" was seven, the minimum zero, mode 3, median 4 and mean 3.8 ± 1.7.

Then institutions surveyed compound a great majority of their radiopharmaceuticals on site. They are known for their practice at the highest level of Nuclear Medicine and Nuclear Pharmacy. Therefore it is possible that these are not representative of every Nuclear Medicine laboratory in smaller hospitals with relatively low volumes of procedures.

Conclusion

This study determined that the health risk of administering radiopharmaceuticals is extremely low. Furthermore, efficacious delivery of optimal Nuclear Medicine services requires departure from the package insert on occasion. This practice has not been shown to have any adverse patient effects.