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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

INFORMAL DISCUSSION OF LITERATURE REVIEWS
OF SAFETY AND EFFICACY
FOR PET AMMONIA AND FDG

Tuesday, November 17, 1998

9:00 a.m.

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(202) 546-6666

PARTICIPANTS

Moderator: Jane Axelrad, Associate Director for Policy,
Center for Drug Evaluation and Research

INSTITUTE FOR CLINICAL PET

Jorge Barrio, Ph.D., Professor, Department of Molecular and
Medical Pharmacology, University of California,
Los Angeles

R. Edward Coleman, M.D., Professor of Radiology,
Duke University Medical Center

Peter S. Conti, M.D., Ph.D., Associate Professor of
Radiology, Clinical Pharmacy and Biomedical
Engineering, University of Southern California

Jennifer Keppler, Executive Director, Institute for
Clinical PET

Ruth Dean Tesar, Vice President and General Manager,
PETNet Pharmaceutical Services, LLC

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Jane Axelrad, Associate Director for Policy

Florence Houn, M.D., M.P.H., Deputy Director,
Office of Drug Evaluation II

Patricia Love, M.D., Director of Medical Imaging and
Radiopharmaceutical Drug Products,
Office of Drug Evaluation III

Victor Raczkowski, M.D., Deputy Director
Office of Drug Evaluation III

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1 P R O C E E D I N G S

2 Opening Remarks from FDA

3 MS. AXELRAD: Welcome everybody to the second
4 meeting to discuss the implementation of Section 121 of the
5 FDA Modernization Act with regard to PET products. I am
6 Jane Axelrad, the Associate Director for Policy in the
7 Center for Drugs and the Chairman of the PET Working Group
8 that has been created in the Center for Drugs to address the
9 implementation of Section 121.

10 I would like to start by going around the table
11 and asking everybody at the table to introduce themselves.
12 Then I would like to ask the FDA staff who are here to
13 introduce themselves as well.

14 DR. RACZKOWSKI: I am Victor Raczkowski. I am the
15 Deputy Director in the Office of Drug Evaluation III.

16 DR. LOVE: Patricia Love, Division Director,
17 Medical Imaging.

18 DR. HOUN: Florence Houn, Deputy Director, Office
19 of Drug Evaluation II.

20 DR. CONTI: Peter Conti, University of Southern
21 California.

22 DR. COLEMAN: Ed Coleman from Duke University.

23 DR. BARRIO: George Barrio from UCLA.

24 MS. KEPPLER: Jenny Keppler from the Institute for
25 Clinical PET.

1 MS. TESAR: Ruth Tesar from PETNet Pharmaceutical
2 Services.

3 [Introduction of staff and audience.]

4 MS. AXELRAD: Thank you. I apologize for the lack
5 of a sound system. The last time that I was in this room
6 which has only been used, I think once before, it was for
7 the Pharmacy Compounding Advisory Committee and there was a
8 sound system here. It sort of happened on its own so I
9 didn't realize that I had to make special arrangements to
10 have a sound system which is why, when we came and
11 discovered there wasn't one, we rearranged the tables so we
12 can all hear each other.

13 But I think we will have to speak up a fair amount
14 so that the people who are on the sides and around the room
15 can hear us. And also for the mikes, there are mikes on the
16 table for the recording for the transcript.

17 This is a public meeting. It was announced on the
18 Upcoming Meetings calendar. Members of the public are
19 invited to attend. However, it is a meeting between FDA and
20 the Institute for Clinical PET. It is a working meeting
21 like the last meeting that we had where we are going to
22 really have a fairly free-flowing discussion, I hope, of the
23 technical issues associated with determining the safety and
24 efficacy of some of the PET products.

25 We will give people in the audience, should anyone

1 else come in, the opportunity to make comments at the end of
2 each topic session. As you can see from the agenda, we are
3 going to start with Dr. Barrio whom I will ask to give some
4 opening remarks. Then Dr. Love is going to give some
5 background on how we have been looking at these PET
6 products.

7 Dr. Houn will give a presentation on the results
8 on the PET ammonia literature review and then we would like
9 to sort of open it up for discussion. Then Dr. Raczkowski
10 will give a status update on where he stands on the review
11 of FDG. Then we will be able to discuss that. Then we will
12 have closing remarks.

13 We will try and break at appropriate times during
14 the morning and we will break for lunch for about an hour.

15 Let's turn to the substance of the meeting. In
16 August, our first meeting of this sort of nature focused on
17 the chemistry of the PET products that are currently in use.
18 I think that we made a great deal of progress in discussing
19 some of the issues associated with what would be needed to
20 address the chemistry of these products and on the
21 specifications that we would be developing.

22 That discussion is going to continue, I believe,
23 at the USP tomorrow where we will be discussing the PET
24 monographs that are in the USP.

25 But today we are going to change our focus and we

1 are going to talk, really, sort of for the first time about
2 the safety and efficacy of some of the PET products that are
3 commonly in use.

4 Our approach to this--as you all know, we were
5 directed by the statute to develop new policies and
6 procedures for the regulation of PET. We felt that it would
7 most appropriate from the agency standpoint to focus on the
8 products that are already in use, most commonly in use, and
9 to see what we can learn from the literature, for which
10 there is extensive literature on some of these products,
11 about their safety and efficacy.

12 So we embarked on a review of the literature for
13 ammonia and for FDG, for additional indications for FDG
14 other than the one for which it is already approved. We are
15 going to update you today on the status of those reviews and
16 where we are so far on those.

17 We feel that after we have gone through this
18 exercise of looking at the products that are commonly in use
19 we will have come to some common understanding of what is
20 needed to demonstrate the safety and efficacy of these
21 products that we can use to start looking at how we will be
22 developing information and approvals for the newer products,
23 the products for which there isn't as much in the
24 literature.

25 So, with that sort of introduction, I would like

1 to ask Dr. Barrio if he would like to make some remarks.

2 **OPENING REMARKS FROM THE INSTITUTE FOR CLINICAL PET**

3 DR. BARRIO: Thank you, Jane, very much. I don't
4 have an awful lot to say except to thank you, thank the
5 staff also on behalf of my colleagues and friends. We have
6 two committee members only here from the original, Dr. Conti
7 and myself, and Jenny, of course, but we also invited to
8 join us Dr. Coleman who has enormous expertise in the area
9 of indications, of course. He is one of the founders of the
10 Institute of Clinical PET. And Ruth Tesar who is the
11 current President of the ICP.

12 We feel that this meeting is of great importance
13 to us because, realistically, there is no point in having
14 wonderful radiopharmaceutical regulations and assumingly
15 easy procedures or regulations for the preparation of the
16 radiopharmaceuticals if we don't get to the final point and
17 that final point is to have appropriate clinical indications
18 established for these radiopharmaceuticals.

19 I think that is, I guess, the overall objective of
20 our exercise here and we are delighted to have the
21 opportunity to work with the agency and solve or resolve
22 some of the issues that are outstanding in this particular
23 area.

24 I think that what happened with PET is quite
25 unusual in many regards, of course. The technique has been

1, available for more than twenty-five years. INDs existed for
2 FDG, for example, since 1976. We have thousands and
3 thousands of papers in the chemistry area, animal models,
4 clinical studies.

5 But what happened was that, as we all know, when
6 the time came for applying PET to the clinic, the agency and
7 the PET community found themselves in a dilemma of how to do
8 this because we didn't have any industry, any support from
9 any angle that is normal for any other drug or any other
10 radiopharmaceuticals.

11 Therefore, we didn't have any clinical trial
12 format for any of this and what we were trying to do today
13 is to initiate a discussion, I guess, that, of course, was
14 initiated several months ago in order to resolve this
15 dilemma and use these five radiopharmaceuticals that we have
16 proposed as examples of what needs to be done in the future
17 for the new ones.

18 Again, on behalf of my colleagues and friends, we
19 would like to ask you for this opportunity, Jane, and your
20 staff.

21 **Background**

22 DR. LOVE: What we are going to do just for a few
23 moments is go over a little bit of background material that,
24 to some extent, is shaping our thinking as we are looking at
25 the PET products and being able to address some of the

1, things that you just mentioned, Dr. Barrio, the idea of the
2 fact that we are somewhat in a dilemma in terms of how are
3 we going to move forward.

4 [Slide.]

5 So we just want to put a little bit of background
6 on the table, so that we are all at least aware of some of
7 the different perspectives as we try to move forward with
8 this. So, a few moments on that. I am going to spend just
9 a little bit of time on some recently published documents
10 and how they may be of assistance to us, and then come to
11 the options that will be considered for the remainder of the
12 day.

13 [Slide.]

14 Normally, from a background perspective, as you
15 were just mentioning, we have a drug development process
16 that goes through a lot of this information, so I will just
17 skip this, since you covered it for me quite well.

18 [Slide.]

19 But it leads to labeling basically, so one of our
20 ultimate goals as we go through all of this process is
21 making sure that at the end of the day, if whatever the
22 process is leads to some type of labeling, that would
23 provide useful information, and the labels generally include
24 some of the information that is identified here on this
25 particular slide, some of the different information that is

1 here.

2 [Slide.]

3 Some of the things, as Jane was just mentioning,
4 we have been talking about the CMC issues, so we won't focus
5 on that. We will be looking at FDG and ammonia as models
6 today, and looking at the published literature, and that in
7 a way is somewhat unique.

8 There are a few examples of where the FDA has used
9 published literature to approve products. Often those are
10 products that have been already on the market and are coming
11 forward as supplemental indications, so it will be unique
12 for us to move forward with approving other products from
13 the very beginning with the literature, but we are working
14 towards finding ways to be able to consider how to do that.

15 Also, what is a little unusual for us today is
16 that often when we are in somewhat of a pre-NDA phase, where
17 you are looking at the data, the sponsor is coming and
18 presenting that information to us, so this type of
19 presentation format is unique for us in the sense that we
20 have been reviewing, and we are presenting it to you and
21 seeking your input and guidance. So, this will be an
22 experimental process.

23 [Slide.]

24 As I mentioned, there are a few documents out
25 there, the guidance document for providing clinical evidence

1, of effectiveness in human drugs and biologics, was published
2 earlier this year, in approximately May of this year, and we
3 tend to refer to that as the evidence document, so if we go
4 through today and use that jargon, that is what we are
5 addressing, but it provides some information that might be
6 useful.

7 There is a proposed rule for in-vivo
8 radiopharmaceuticals used as diagnostics or for monitoring,
9 and there is our recent guidance that was just published for
10 developing medical imaging agents. These are things that
11 are perhaps affecting some of our thinking.

12 They are starting points, they are not ending
13 points, and it can help us as we move through this.

14 [Slide.]

15 Just a couple of things. Although this guidance
16 for the evidence document provides a lot of information for
17 sponsors who are starting at the beginning part of the
18 process, what I just wanted to mention for today is the
19 published literature aspect of this.

20 There is a brief section in that guidance that
21 talks about approaches to using published literature.
22 Particularly, one might look for multiple studies that are
23 conducted by a number of different investigators that have
24 common or similar designs, that allows us to have and find
25 information that presents consistent results.

1 Another is the articles generally have a high
2 level of detail that will allow us to clearly identify what
3 the protocol is, how the patients are entered, what is the
4 plan for the statistical analysis, and they have objective
5 endpoints that are useful for the proposed indications that
6 are under consideration.

7 [Slide.]

8 Also, the guidance noted that there be results
9 generally come from the prospective planned analysis as
10 opposed to an analysis that might be developed post hoc.
11 So, we look at these articles from that perspective, and, of
12 course, one looks at the credibility of the authors and the
13 particular site because we don't generally have the
14 opportunity to inspect the studies as we might normally do.

15 So, these are things that we are thinking about
16 that might be able to be considered.

17 I won't spend a lot of time on the proposed rule.
18 The comment period for that did just end, but we do expect
19 that there may be some related comments that still come in
20 with the guidance document.

21 [Slide.]

22 You are familiar with these definitions, I am
23 sure, and they certainly fit with some of the PET products,
24 but whether PET is going to be part of the proposed rule for
25 radiopharmaceuticals or how that is going to be worked out,

1, and is it going to be a separate set that addresses this is
2 still yet to be determined.

3 [Slide.]

4 One of the things that the proposed rule does
5 address is a set of indications that can be sought for
6 radiopharmaceuticals, approaches to the evaluation for
7 effectiveness, and also for safety. Today, we are primarily
8 going to talk about effectiveness.

9 [Slide.]

10 These things were amplified primarily in the
11 guidance for industry, for the draft for developing medical
12 imaging and for drugs and biologics, and I don't want to
13 spend a lot of time going over the details of the guidances.

14 [Slide.]

15 You do have them with you, but I did want to
16 mention just briefly the comment period closes on December
17 14th, so please, if you have some comments that are relating
18 either to PET or anything in general, please get those to
19 us.

20 [Slide.]

21 The other is that the indication area is probably
22 most relevant for some of our discussions today. The
23 guidance talks about different groups of indications,
24 structural, functional, physiologic, or disease or pathology
25 detection, or something that is going to be used for

1, diagnosis or therapeutic management, and that means
2 diagnostic management in a series of workups or patient
3 therapeutic management.

4 Our approach to putting that information there is
5 in response to questions that often come to us for how would
6 one work up a product for a particular use, and those uses
7 tend to fall into these different categories.

8 Today, we will be looking at that perhaps from the
9 flip side, saying what is the information that we have, does
10 it fit in one or more of these categories. We certainly
11 recognize that there are multiple categories and overlap of
12 different types of indications that often makes best sense,
13 so we will be looking at that.

14 [Slide.]

15 This brings us back then to our focus for today,
16 that is on the safety and efficacy of these commonly used
17 products, particularly looking at FDG and ammonia as a
18 model. As I mentioned, and as Jane has also talked about,
19 we will be look at the literature. We also have support
20 from various reviewers who are in the audience, who have
21 been looking at the pharmacology, the pharmacokinetics, and
22 pharmacodynamics information which also might be of great
23 assistance to us as we work towards this.

24 Dr. Raczkowski and Houn will be talking about some
25 of the information that they have gleaned from the different

1 articles and again looking at all of this to get to the
2 indication considerations that will be discussed as the
3 remainder of the day progresses.

4 I am going to stop there. Are there any questions
5 or comments? This is really just background material.

6 Yes.

7 DR. COLEMAN: I think, as you had pointed out, Dr.
8 Love, and Dr. Barrio pointed out, that this has been an
9 ongoing struggle to figure out where PET fits in, and is one
10 of the reasons the statute was written.

11 I remember meeting several years ago with Dr. Pet,
12 and he asked us several questions, how many people died from
13 ammonia and FDG. We said none. How many people have been
14 admitted to a hospital because of injection of FDG? None.
15 How many adverse reactions have occurred from ammonia and
16 FDG? None.

17 He said, well, you would think we would be able to
18 evaluate this differently than other drugs. And that has
19 been the struggle, and I think that is why we are here
20 today, because there has not been a mechanism for evaluating
21 these extremely safe radiopharmaceuticals -- I hate to call
22 them drugs because that has a connotation to you all that we
23 don't like -- but has some regulatory mechanisms that are
24 inherent in that term.

25 But I think there needs to be this way that you

1, are working on to look at these tracers different than
2 drugs, and hopefully, that can come about based on what is
3 in the literature and then going forward to develop a new
4 mechanism for looking at these very safe group of compounds.

5 DR. LOVE: Right. We certainly agree that it is
6 very important for us to look at this, and both Drs. Houn
7 and Raczkowski will talk about some approaches in the actual
8 review and what we have been trying to do to pull together
9 the different parts of the literature. They will be
10 presenting primarily the clinical perspectives on this. As
11 I mentioned, we are looking at other supportive information
12 from the preclinical and from the pharmacokinetics,
13 pharmacodynamics information.

14 Particularly, it is useful if we are thinking
15 about metabolic processes and what has been demonstrated
16 from those. So, yes, the purpose of my comments simply is
17 to give some of the framework, some of the thoughts, some
18 information that is useful to us, but it is not our stopping
19 point, and there is other information that will be coming
20 and getting on the table as we go on today.

21 I think the details will come from their
22 presentations.

23 DR. COLEMAN: I think that one concept I would
24 like to get to is -- and I think this is the purpose of the
25 statute -- is to not be grounded in what has gone on in the

1, past, where can we go to the future, that these are
2 different than other drugs that have typically been handled
3 by the FDA, and how do we get this through the difference
4 here to come to a structure that will work for these
5 radiopharmaceuticals in the future.

6 So, I think that focusing on the past and regular
7 drugs, we will learn from that, but we need to move forward
8 to look at a different process as we go forward here, such
9 as you are doing.

10 I think that one of the things that we should try
11 to keep in mind as we go forward today is to try to clarify
12 exactly in which ways PET drugs may be different from other
13 radiopharmaceuticals or from any drugs in general and how
14 that might affect the drug approval, but I think if we can
15 get down just some concrete things and characteristics of
16 these products that can distinguish them, I think that will
17 be very helpful.

18 MS. AXELRAD: I sort of view it as we have sort of
19 one foot in the past and one foot in the future for this.
20 You know, we are not turning our back entirely on what we
21 always do, but we are trying to address these, you know, in
22 a different way within the constraints of the statute and
23 everything, so we are not totally changing, but I think that
24 we are straddling the line and trying to move forward in
25 that way.

1 DR. CONTI: I have sort of a housekeeping
2 question. There are a number of these guidances and
3 proposed rules that are coming out. I think one is actually
4 there was a November 16 deadline that has now come and gone,
5 and we have got another December 14th guideline that is
6 facing us.

7 We are in a bit of a quandary here because we are
8 trying to formulate how we are going to deal with the
9 chemistry and the clinical side of PET radiopharmaceuticals,
10 yet, we have documents that are sort of passing us by in
11 this process, so we are not sure whether to respond to these
12 documents, how to do that, because we haven't structured our
13 type of approach to it.

14 What would you recommend we do here?

15 MS. AXELRAD: What I would recommend, I think in
16 both of the documents, both the proposed rule and the
17 guidance document, we indicated that they didn't directly
18 apply to PET, and how they might be applied to PET in the
19 future remained to be determined, which is what Dr. Love
20 said.

21 What I would suggest is that you focus on the
22 documents and comment on them to the extent that they
23 present problems for you. If you feel that there is
24 something in there, that if it were applied to PET would be
25 problematic, I think it would be good if you would bring

1, that to our attention.

2 I think that certainly the proposed rule and the
3 guidance document, which is actually a bigger elaboration,
4 represent the Agency's current thinking on how they view the
5 indications for diagnostic pharmaceuticals, of which PET is
6 one, and we try to articulate that and to clarify what our
7 thinking is in a way that we felt would make it less
8 burdensome for all radiopharmaceutical diagnostic products
9 that come to the market, because we felt that people out
10 there believe that they have to demonstrate quite a bit more
11 than may really be necessary to get an approval, and we
12 tried to indicate by breaking down those indications that
13 what you are going for, what kind of an indication you are
14 trying to get determines what kind of information you have
15 to supply.

16 It is sort of like a hierarchy from a sort of
17 lowest of the sort of a functional claim to a patient
18 management claim that determines the level of information,
19 and I think that that thinking would apply to PET diagnostic
20 pharmaceuticals, as well, and so I think you should look at
21 both of those documents and comment on them about how they
22 would affect you if they were to be applied or what problems
23 that might cause if they were applied to PET, and then we
24 will do some more talking later on in this process. We will
25 be having other meetings like this where we can talk more

1, specifically about what comments you make and where we are
2 going in terms of finding those documents in the PET arena.

3 DR. CONTI: My concern is the deadlines, and it is
4 the issue of as we proceed through these discussions, it
5 becomes clearer what the consensus is going to be, and then
6 going back again, re-reviewing the documents, what may have
7 been cited as a problem originally is no longer a problem,
8 or what was not decided to be a problem, is now a problem,
9 and the deadline is already past, so this is a concern that
10 I have, just in terms of the iterative process that we are
11 going through here and the deadlines that we are facing for
12 responding.

13 So, I don't know how to address that.

14 DR. LOVE: I think the other thing about the
15 guidance document, particularly the last one that went out,
16 that one is an overall guidance for prospective development,
17 so you are looking at this from two different perspectives
18 at the moment. We have a set of questions on the table
19 right now for the commonly used products and how we can
20 address them, and then the other part is what about
21 prospective development, new products coming down the line.

22 So, you might want to think about it from that
23 perspective. The other document gives us, as I said,
24 starting points for literature, but those are very general
25 points. There is flexibility in how one might use the

1, literature, and it really depends upon the literature and
2 what the literature says, because that is more retrospective
3 use of data. So, they are different perspectives.

4 But even though the comment period for the
5 radiopharmaceutical rule has closed, there are implications
6 of that in the guidance, and certainly address your concerns
7 in that context.

8 MS. AXELRAD: The way it is set up, neither of
9 them actually applies to PET right now, so I think that we
10 have left it open to see whether there are parts of it that
11 would be applicable to PET or whether we need to do a new
12 rule and a new guidance that would be unique to PET, and so
13 I think that as we go down the path we can do that.

14 Also, comments on the guidance comments, even
15 though we have a -- whatever it is, 90-day, do we have a 90-
16 day or 60-day on the guidance -- 60-day comment period on
17 the guidance document, and we do that because we want to get
18 the comments in, and we want to finalize it, we have a
19 statutory deadline to finalize the rule by May 21st, or
20 whatever it is, of '99, and we would like to have the rule
21 and the guidance document finished at about the same time,
22 but the Agency's position is that comments are welcome on
23 guidance documents at anytime, and even after we issue a
24 final guidance, people are still free to comment and say
25 that it needs to be changed in some respects, and it is sort

1. of an iterative process. Obviously, once we finish one, we
2 don't want to open it up the very next day, but if we get
3 comments, we will consider them and decide whether it would
4 be appropriate to revise it.

5 But I think, you know, obviously, it is going to
6 be an open question how those things are going to apply to
7 PET is open as far as we are concerned, and we will talk
8 through that and see what happens, but it would be good to
9 get your comments, because it may be that there are some
10 small things that could be taken into account while we are
11 drafting either the final rule or the final guidance
12 document that would obviate the need for having a separate
13 document for PET.

14 So, to the extent that you can communicate with us
15 on those, it would be helpful.

16 MS. TESAR: I would like to make a comment. One
17 thing that would be very helpful to us to going forward, and
18 I am not sure if it is this meeting, I would hope that it
19 would be this meeting because I think it has a bearing on
20 where we go for indications, is a discussion or some
21 guidance on exactly what the various levels of claims mean,
22 and what that means to a commercial product or the industry
23 or to the users. I think it is somewhat new to us, and
24 discussion of the levels of claims and what that would mean
25 going forward would be extremely helpful when we are looking

1 at how we want to look at our indications.

2 MS. AXELRAD: I think I would like to hold that
3 until after we go through the ammonia and the FDG reviews,
4 because I think that some of the discussions that we are
5 going to be having around those will illustrate in much
6 more, sort of concrete terms how we are applying that sort
7 of indication structure, and what we think the literature
8 supports and what we think it may not, and then we can talk
9 about that after having gone through that discussion, if
10 that is okay with everybody.

11 DR. COLEMAN: Just one comment. You produce
12 guidances for industry. The PET radiopharmaceuticals now,
13 and in the future, probably won't come through industry. I
14 am not sure what that means related to these types of
15 documents, but it is just something, as we go forward, this
16 is going to be need to be kept in mind.

17 MS. AXELRAD: That is a generic term. The Agency
18 has two types of guidance, guidance for industry and
19 guidance for reviewers, and we had this come up. We were
20 working on a guidance on pharmacy compounding, and somebody
21 suggested that it should say guidance for compounders
22 instead of guidance for industry, but we decided to leave it
23 as guidance for industry because in this case, the
24 compounding industry is the industry, and in this case, the
25 PET community is the industry.

1 DR. COLEMAN: So, an individual, it could be an
2 industry.

3 MS. AXELRAD: Well, they are a small industry
4 perhaps, a cottage industry maybe, but they are the other
5 side of the table as far as we are concerned, it's the FDA
6 and whoever it is that we are regulating.

7 We had the same thing on the Pharmacy Compounding
8 Advisory Committee, we had an industry representative.
9 Actually, we have two industry representatives, one
10 representing the traditional pharmaceutical industry and one
11 representing the compounding industry, so we had to split
12 the term to fit the situation.

13 **Presentation of PET Ammonia Literature Review**

14 DR. HOUN: Good morning. I am Florence Houn. I
15 am the Deputy Director for the Office of Drug Evaluation II.
16 I am also an instructor in oncology at the Johns Hopkins
17 School of Medicine, and Co-Director of the Breast Ovarian
18 Surveillance Service at Johns Hopkins Oncology Center.

19 [Slide.]

20 I am going to be talking about my safety and
21 effectiveness review that I did along with Sonia Castillo,
22 who is our statistician, who has been at FDA for three
23 years, and she got her Ph.D. at the University of
24 Washington, Seattle, and did her postdoctorate at the School
25 of Public Health at Harvard University.

1 [Slide.]

2 I also want to let people know that we have a team
3 working together on ammonia. These are the members of our
4 team. We have chemists, pharmacists, all sorts of expertise
5 that I drew upon to do my review.

6 [Slide.]

7 The first thing I want to let people know is our
8 conclusions, and we did go through the literature and found
9 that for effectiveness, an indication would be for N-13
10 ammonia to assess myocardial perfusion. We also found that
11 there was safety in the doses that were used. In the
12 literature, it was anywhere from 8 to 25 mCi studied, and
13 there were also studies that showed 1 I.V. doses, usually
14 separated between 30 and 40 minutes.

15 [Slide.]

16 So, how did we do this review? Well, we
17 structured our review in terms of looking at the guidances,
18 looking at existing policies on what is effectiveness, what
19 is safety. We looked for an intended use for ammonia. We
20 looked at external standards of how to compare studies.

21 We looked at many studies. Some of them were
22 purely investigational, others were comparative to allow us
23 to understand how it performs relative to a drug that we had
24 a diagnostic performance already established for.

25 We also developed a search methodology, which I

1 will talk about. We developed selection criteria for
2 articles. I am going to review our findings and
3 particularly talk about one article which we found very key
4 in bolstering and supporting effectiveness, and our
5 conclusions.

6 [Slide.]

7 This is, of course, the effectiveness document
8 that Dr. Love had talked about, and it was important that we
9 were able to find multiple studies in the literature about
10 N-13 ammonia and myocardial perfusion. We found that the
11 study designs were adequate and there were consistent
12 findings across many studies, many institutions, and across
13 time.

14 We also were very impressed by some articles
15 having very detailed study protocol and study results
16 presented. We looked at how the comparison was made between
17 N-13 ammonia perfusion and to their external standard of
18 truth, such as coronary angiograms or the quantitative
19 angiograms.

20 We looked at the consistency of conclusions, and
21 we looked at how the studies were conducted, whether there
22 were efforts to minimize bias including randomization or
23 masking of clinical data, and this procedure has been used
24 before by FDA. Secretin was used. The literature was used
25 to evaluate pancreatic function. Bleomycin and talc were

1, approved for malignant pleural effusion indications using
2 the literature, and doxycycline was reviewed in the
3 literature to get an approval for treatment of malaria. So,
4 this process has been used before.

5 [Slide.]

6 We looked at the medical image guidance, which is
7 a draft guidance out, and it outlined some points in terms
8 of what to look for in adequate and well-controlled studies.
9 Particular attention should be paid to selection of
10 subjects, are the subjects who are studied part of the
11 target population for which the test is being intended to be
12 used.

13 We looked whether the readers of the imaging
14 tests, the reading was done independently, masking,
15 randomization, whether reading was done separately. We also
16 looked at the standards of truth, endpoints, analysis plans,
17 and what was written about safety.

18 [Slide.]

19 We selected the intended use to assess myocardial
20 perfusion based on a preliminary review of the literature
21 and the fact that this turned out to be, we think, the major
22 use for the product was an important use, and that there was
23 enough literature written that either related directly to
24 assessing myocardial perfusion or tangentially to it, that
25 we could draw on other articles to support this indication.

1, In looking at the Medical Imaging draft guidance,
2 this indication of to assess myocardial perfusion, we were
3 looking at it as a functional assessment indication, and
4 that there were standards of truth to perfusion, that the
5 study subjects that we saw in the literature did represent
6 the spectrum of disease that the radiopharmaceutical would
7 be used in, and this functional claim of perfusion, we knew
8 that ammonia, it is almost linearly related to flow over
9 between zero and 300 cc's per minute per 100 grams of
10 tissue, so we found there was a functional pharmacologic
11 basis for it to be able to detect flow.

12 [Slide.]

13 Looking at external standards, we understood that
14 a lot of studies were used in comparison to angiography, and
15 there are problems with angiography. The writers did
16 acknowledge that using things like percent diameter
17 narrowing didn't really address things like diffuse disease
18 or the viscosity of blood or takeoff angle, so it is a two-
19 dimensional standard, but what has been developed through
20 use of computerized programs and algorithms are allowing for
21 a more quantitative evaluation of flow using angiographic
22 information. So, that was very, very useful.

23 We also knew that rubidium had been approved by
24 FDA for flow and that there were also studies in the
25 literature using rubidium as a standard.

1 In trying to understand myocardial perfusion, it
2 is not just outlining of anatomy, looking at large vessels.
3 We knew there was this area of microperfusion that PET
4 products certainly were able to detect, and in trying to
5 evaluate what is the external standard for microperfusion,
6 we looked at some functional aspects, such as wall motion,
7 functional capacity on stress testing, and even clinical
8 outcome studies.

9 [Slide.]

10 Our search criteria, we asked for an on-line
11 search from January 1, 1990 to July 1, 1998 for all human
12 clinical trials articles published in English from the
13 listed databases, that had to do with ammonia and myocardial
14 perfusion.

15 We also got articles from ICP suggestions, and we
16 also looked at references from the above articles that we
17 found.

18 [Slide.]

19 We selected articles based on the fact that there
20 was a comparison to an external standard of truth, that the
21 questions the articles had as main study hypothesis were
22 relevant to myocardial blood perfusion, that they had well-
23 described study populations, and that there were procedures
24 to reduce bias, especially earlier on when more inter-
25 observer variability issues had to be dealt with in medical

1, practice.

2 [Slide.]

3 From this literature search we came up with a
4 total of 17 articles, of which we found that two, the two
5 articles that we felt were very well written, well supported
6 in terms of adequate and well-controlled trial criteria,
7 they are related to each other.

8 One was a preliminary study and another one was
9 the follow-up, longer term study. We also found that there
10 were other controlled published studies that were supportive
11 and other published studies that had a wide variety of study
12 hypotheses, but that were also contributing to understanding
13 performance of N-13 ammonia and myocardial perfusion.

14 We also looked at some articles that dealt with
15 the quantification algorithm that is used for N-13 ammonia.

16 [Slide.]

17 So, for the two studies that we are going to spend
18 more time talking about, there is a study by Dr. Gould,
19 published in '86. This was a preliminary study, and the
20 follow-up study was by Dr. Demer, published in 1989.

21 [Slide.]

22 The other controlled studies that we have listed
23 are Schelbert 1982, Di Carli 1994, Gewirtz 1994, and then we
24 have about nine other supportive studies that are just
25 listed here in alphabetical order.

1 [Slide.]

2 These were the studies that we used to look at the
3 quantification of blood flow.

4 [Slide.]

5 I am just going to briefly talk about the Gould
6 article and spend more time on the Demer article.

7 The Gould article was a feasibility study for
8 diagnosing coronary artery disease with rubidium and
9 ammonia, and it used the rest and stress test format with
10 pharmacologic stressing.

11 The sample size for ammonia was small, 23 out of
12 the 50 patients received ammonia, and the results were not
13 broken up, were not stratified by radiopharmaceutic agent,
14 although there were some comments in the paper in general
15 that both ammonia and rubidium had similar performance.

16 The design was prospective in that the folks that
17 came to get this test were being enrolled and were actively
18 going for coronary angiography. The study had masking, and
19 the results were reread three times. The study did provide
20 dose, and the definitions on what was significant for
21 coronary flow reserve was defined.

22 What was a little bit, though, unclear was the PET
23 results were presented in isocounts, and I am assuming from
24 reading the captions and the figure comments that the
25 percent isocount reduction was proportional to the decrease

1, in CFR.

2 The preliminary results showed that 21 out of 22
3 patients were identified by PET who had coronary angio-
4 diagnosed disease, and the specificity, 9 out of 9 for
5 people who had negative PET tests, as well as negative
6 coronary angiograms.

7 [Slide.]

8 In terms of the Demer tests, the Demer article, it
9 specifically had the hypothesis that it was going to
10 evaluate accuracy in ammonia PET test, compared to coronary
11 angiography, again using the rest/stress format.

12 In this case, about 111 patients out of 193
13 received ammonia. This was a significant number of patients
14 receiving the radiopharmaceutical that we were interested in,
15 and we also noted that the analyzed data only considered 174
16 cases, 19 patients who had infarct-related stenoses, would
17 have undergone acute vascularization, were excluded because
18 there was concern that the residual stenosis severity would
19 not be comparable to the PET perfusion defect.

20 The inclusion criteria were all patients
21 undergoing catheterization, and these patients included a
22 wide variety, people with unstable angina, people with known
23 coronary artery disease, people with suspected coronary
24 artery disease, and so this population was what we thought
25 would be relevant to the actual intended use population for

1 N-13 ammonia PET tests.

2 The design was comparing stenosis flow reserve,
3 which was an automated quantitative result, versus PET
4 perfusion defect scores, which were qualitatively
5 subjectively derived.

6 [Slide.]

7 Scales for stenosis flow rate were presented from
8 zero to 5, 5 being normal, and anything less than 3 being
9 significant for coronary artery disease, and for PET
10 perfusion defect scores, the range was also zero to 5, but
11 in the opposite direction, 5 being severe perfusion defect,
12 and anything greater than 2 was considered significant
13 coronary artery disease comparable to an SFR of less than 3.

14 Image protocol was outlined and was sufficiently
15 detailed that we felt we understood what happened to these
16 images. There was detail about scoring of the two
17 observers, interobserver variation was tracked, dispute
18 resolution was described. So, there was a lot of detail on
19 how the image protocol was managed. The dose was presented
20 in the paper.

21 [Slide.]

22 The results were presented as a Spearman
23 Correlation Coefficient where the most severe stenoses of
24 each patient -- and some patients had more than one stenoses
25 -- so they took the most severe ones and compared the PET

1 score with the SFR score, and they found very good
2 correlation.

3 There was a statement in the study that for the
4 193 patients, there were 2 false positives and 7 false
5 negatives, and this article broke down in terms of the
6 performance of each agent, rubidium versus ammonia, how the
7 false positives and false negatives laid out.

8 So, this was very informative information. This
9 is the kind of information in a traditional NDA we often ask
10 sponsors to provide. This was provided in the article.
11 This information, however, as I show you and I discuss a
12 figure 3 that presents some of the patient data, I wasn't
13 able to recreate totally in terms of the false negatives and
14 false positive data.

15 [Slide.]

16 So, in trying to understand the performance of N-
17 13 ammonia PET in comparison to coronary angiography, what I
18 did was I took figure 3 that they had in the article, and
19 figure 3 is provided to you in a handout separate. You may
20 have that, and I will also show a slide of it, as well.

21 We took figure 3 and tried to derive exactly what
22 the authors were trying not to do. Instead of having a
23 dichotomous scale of disease/non-disease, this article's
24 strength was that it tried to have continuous scales of
25 disease, and what we did was the opposite. We tried to make

1, it dichotomous in terms of putting things in a 2 x 2 table
2 and trying to derive sensitivity and specificity.

3 I am going to ask Kim to turn the slide on.

4 [Slide.]

5 We will just have this slide on briefly. This is
6 figure 3. The bottom here are patients. The top are
7 vessels. That total number of patients studied was 174, and
8 in terms of orientation, this is the PET scores going from
9 zero to 5, zero being no disease, 5 being a very severe
10 perfusion defect, and here is the angiographic results on
11 stenosis flow rate, going from zero to 5. Anything that is
12 less than 3 is considered significant coronary artery
13 disease with a low flow reserve rate.

14 [Slide.]

15 So, what we tried to do with this figure is to
16 derive 2 x 2 tables, and this is the table that we made to
17 correspond to the figure 3. So, what we did was if you look
18 at for stenosis flow rate less than 3, this is considered
19 the disease using the gold standard, there was a total of 96
20 patients, which are the same 96 patients that, on the column
21 to your left, you see me outlining the total number of
22 patients who have a flow rate of less than 3.

23 So, we have a total of 96 people with significant
24 coronary artery disease. The remainder, the 78, are people
25 with a flow rate of greater than or equal to 3, and then for

1, PET scores of greater than or equal to 2, that was
2 considered diseased, and we looked on the figure and looked
3 where the dashed line is. To the left of that are the 68
4 patients who had a score of less than 2, considered to have
5 a negative PET scan, and the patients to the right of that
6 dashed line are 106, and those are considered to have a
7 positive PET scan.

8 So, we now have the totals for the rows and
9 columns for a 2 x 2 table, and this is a table where there
10 is 1 degree of freedom. If I put one number in a box,
11 everything else must add up accordingly to get the rows and
12 columns totals.

13 So, what I did was I looked at the false positives
14 and the false negatives. Those are squared boxes in this
15 diagram. The squared box to the left of the dashed line
16 refers to patients who have a low PET score, meaning that
17 the PET scan is saying they are disease-free, and yet if you
18 go above a stenosis flow rate, scores of less than 3, this
19 is considered diseased by angiograms, and so this box here
20 refers to the false negative people who were told they were
21 negative by PET scan, but on angiogram were positive for
22 disease.

23 This box here refers to the false positives,
24 people who on PET scan had a high score, over 2, but on
25 stenosis flow reserve calculation, had a score of less than

1 3. Those are error bars, and the actual patient numbers are
2 right by the error bars in the diagram.

3 We decided that in choosing this error bar, and
4 estimating that two out of four of those patients were false
5 positives, we put the number 2 here, and that gave us the
6 rest of this table.

7 So, that was how we derived the 2 x 2 table to try
8 to calculate sensitivity and specificity for patients.

9 Now, it doesn't actually fit because the article
10 actually said that there were 7 false negatives and 2 false
11 positives, so these numbers do not mesh with what was
12 presented in the article. However, the article, 2 false
13 positives and the 7 false negatives were derived from an n
14 of 193, and not 174, so some of the people that were
15 excluded from the analysis have to be taken into account,
16 and this is where, when we don't have NDA data and line
17 listings of each patient in the literature, we are making
18 some assumptions.

19 The assumptions we made, we tried to be consistent
20 across the patient diagram, as well as the vessel diagram,
21 which I am going to show next.

22 [Slide.]

23 This is for the vessel diagram. We did the same
24 type of procedure in terms of getting the rows and column
25 totals, and then estimating the error bar for a false

1 negative exam.

2 [Slide.]

3 So, in looking at the totals, we find that it
4 derived a sensitivity of 98 percent for patients, a
5 specificity of 85 percent. We divide the 95 percent
6 confidence limits, and we did the same for vessels.

7 DR. CONTI: What assumption do you make about the
8 gold standard with regard to its accuracy in doing this
9 analysis?

10 DR. HOUN: Well, we do know that in looking at
11 perfusion, PET products are not going to give the same
12 results as angiographic results, and we have some of the
13 articles that actually show contradictory results, where the
14 angiograms will show collaterals, and the PET scores will be
15 different, and in trying to resolve that, we are defining
16 perfusion, not only in terms of an anatomical definition
17 which is something that angiography is more consistent with,
18 larger vessels or medium-size vessels, and looking at
19 anatomical characteristics where there is stenosis.

20 We also have to take into account this aspect of
21 microperfusion, which angiography may not reveal, and yet
22 the PET test may show that there actually is perfusion.

23 In this case, the correlation was very good, and
24 that is I think because they are looking at these larger
25 vessels. They are not so much concentrating on an area

1, where some of the other hypothesis in the papers will lead
2 to more prominence of microperfusion aspects.

3 So, in this paper, the correlation actually ended
4 up very well. So, when we are looking at the gold standard,
5 we understand that the gold standard has its limits. It is
6 a consensus-derived standard, and it is a standard that
7 evolves with more technology. For microbiology, you know,
8 culture used to be the gold standard, and now they are
9 looking more at DNA amplification tests as a gold standard,
10 so they evolve.

11 DR. CONTI: Let me follow this up then. We have
12 chosen this article as sort of representative, in part
13 because of the anatomical gold standard here and also
14 because the correlations are actually quite good and
15 demonstrative.

16 What about correlation with another microperfusion
17 assay as a better gold standard, and would that change the
18 categorization of many of the other papers that have been
19 looked at?

20 DR. HOUN: Well, if we go through some of the
21 papers, you will see from Di Carli that there is evidence to
22 support the microperfusion aspect, and that is why we did
23 find at the end, we do conclude that myocardial perfusion,
24 not just large vessel perfusion, but also some of the more
25 microperfusion functional aspects are supported.

1 DR. CONTI: That is kind of why we do the test
2 actually is the microperfusion issues in large measure. So,
3 it is important to understand that choosing the gold
4 standard here is fine, this is perfectly -- I am sorry --
5 choosing the gold standard as large vessel disease
6 demonstrated on angiography, while potentially appropriate
7 for certain patient populations, is not necessarily the
8 primary indication of why we would do a stress test, let's
9 say. We are in large measure looking for microperfusion
10 changes that may occur.

11 So, my concern is that selection of the gold
12 standard may be something that we need to address a little
13 bit more in detail.

14 MS. AXELRAD: I think that that is always an issue
15 for any diagnostic product is what is the gold standard, but
16 in this case, since the bottom line is that the literature
17 would support an indication for myocardial perfusion, and it
18 isn't limited in any way to large vessel perfusion or
19 something like that, does it really matter here?

20 DR. CONTI: I am just looking at this not this
21 specific, I am trying to generalize because we are going to
22 be talking about a lot of other things over the course of
23 the day, and this is an important concept to understand.

24 DR. LOVE: Maybe just one other comment. When we
25 look at the radiopharmaceuticals in general, often we come

1 up with the issue you are raising, because we recognize that
2 the coronary angiography study is primarily a gold standard
3 for the presence of coronary artery disease, and it does
4 give us some idea of where that disease is and the
5 distribution of the disease.

6 Then, when we look at a radiopharmaceutical that
7 is looking at microperfusion, smaller vessels or some other
8 aspect, then, we are making a correlation in general with
9 whether the angiographic standard for the presence of
10 disease shows us or correlates with the presence of the
11 microperfusion defect, and are they in the same
12 distribution.

13 So, when we analyze these data, we are actually
14 looking at a combination of different things to come to the
15 bottom line of whether or not you are looking at
16 microperfusion. So, it is a combined set of information,
17 both looking at a standard of truth for the presence of the
18 disease, as well as control agents which may also give us
19 information on perfusion, or looking at clinical outcomes
20 and what we are calling here a clinical outcome meaning a
21 wall motion abnormality that reverses, ejection fraction
22 that changes, that sort of thing, so we take a full
23 combination of pieces of information.

24 DR. HOUN: And we have studies that we looked at
25 here that do support the functional aspects, and they

1, compare to stress test performance, improvement in the Bruce
2 protocol or wall motion study, so we looked at those other
3 standards, as well as the PET result in trying to derive
4 support that, in fact, this microperfusion is supported in
5 the literature.

6 DR. RACZKOWSKI: I think that the point that Dr.
7 Conti raised is a very fundamental one that we often deal
8 with, with many diagnostic agents, really trying to
9 determine when does an agent or another modality cross the
10 line and become a new gold standard.

11 That evolves as technology and science evolves.
12 The other area is what you do if there is no gold standard,
13 and these are very difficult problems, and perhaps later we
14 can discuss them more. They are addressed on some level in
15 the guidance document, as well, the draft Medical Imaging
16 guidance document that was published.

17 [Slide.]

18 DR. HOUN: In terms of the Demer study, the
19 strengths laid in the inclusion criteria were highly
20 reflective of the target population. They used a continuous
21 endpoint for PET perfusion defect, as well as for flow
22 reserve. Images were read by two readers independently.
23 They were masked to the clinical data.

24 Interobserver differences in scoring of PET images
25 were tracked and analyzed. There was enough graphical data

1 to allow us to look at individual patient information.

2 [Slide.]

3 There was dispute resolution discussed. There was
4 detailed information on readers' performance and on reader
5 variability. The use of flow reserve for coronary perfusion
6 as opposed to percent area stenosis, and there were also
7 large numbers of patients in this study. This was the
8 largest study that we looked at, and it certainly was
9 impressive for that reason.

10 [Slide.]

11 The weakness of the studies was that it did not
12 segregate the rubidium and ammonia results. The age and sex
13 distribution of results were not given. These are kinds of
14 things that if we had line listings of patients, we would be
15 able to easily look at, and we did recognize that 19
16 patients were excluded from the analysis.

17 [Slide.]

18 Other controlled studies that were supportive was
19 the 1982 Schelbert study that was also a comparison between
20 angio and PET in terms of large vessel disease, coronary
21 artery diagnosis.

22 This study utilized patients who were already
23 diagnosed with coronary artery disease on angiogram, as well
24 as normal volunteers who did not undergo angiograms, but
25 were assumed to have normal anatomy. So, the sensitivity

1 and specificity that were derived from this study were very
2 similar to the Demer study.

3 [Slide.]

4 Di Carli here in 1994 published a paper on the
5 relationship of collateral blood flow, wall motion, and
6 viability, and this term "viability" was defined as
7 metabolism of 18-FDG.

8 What this study was trying to look at was to
9 compare the results of angiography of coronary flow, wall
10 motion, and N-13 perfusion with FDG metabolism, and the
11 results of this study showed that 58 percent of
12 angiographically defined collaterals had low N-13 ammonia
13 flow and that 50 percent that had no collaterals shown on
14 angiograms actually had N-13 perfusion.

15 This was one of the studies that we looked at in
16 terms of addressing the capacity that PET provides different
17 information from angiograms, and that the issue of
18 microperfusion here comes through about -- we are looking at
19 different things.

20 [Slide.]

21 This other study by Gerwitz in 1994 was to
22 determine a minimum level of perfusion needed to sustain
23 myocardium, and it looked at different zones of infarction
24 and healthy myocardial tissue to determine if there was
25 different flow rates associated, and what they did find was

1 a correlation between flow, perfusion as detected by PET,
2 and areas of wall motion, infarcted zones, areas that had
3 poor wall motion had low flow compared to normal wall motion
4 studies and the PET flow rate scores.

5 This study just added to our understanding of the
6 results of biologic consistency in terms of using a
7 different standard here, wall motion, looking at infarct
8 areas, and supporting that PET is able to provide
9 information that is consistent with our understanding of the
10 medical framework.

11 [Slide.]

12 We also looked at other published studies, nine of
13 them, and I am not going to go through all of them, but they
14 had various hypotheses. Some of them were to compare
15 myocardial blood flow to angiography directly.

16 [Slide.]

17 Others of them were to study other kinds of
18 issues, such as flow rate responding to exercise,
19 cholesterol, diet control, conditioning, and these studies,
20 because of their widely variably hypotheses, helped
21 contribute to our appreciation of what PET can do in a
22 variety of situations in terms of assessing myocardial blood
23 flow, not only in terms of the larger and medium-size
24 vessels, but also in terms of a functional approach.

25 [Slide.]

1 So, in doing this review of the literature, one
2 thing that we commented upon in terms of weakness of doing
3 literature reviews is that a lot of the studies, although
4 they may have stated in their original scientific protocol
5 to get IRB approval, they might have had, you know,
6 statistical power calculations with the a priori statement
7 of what Type 1, Type 2 error they wanted to have or what
8 type of correlation would be acceptable or not.

9 Those kinds of things don't get translated into
10 the published literature. It doesn't mean that the studies
11 don't have them, it just means it is just not available for
12 us to read in the literature.

13 Another weakness that we encountered were that
14 many studies were small numbers, 10, 20, 30 patients, but by
15 looking at them as a whole, we got an appreciation for N-13
16 ammonia PET performance.

17 I talked before about the absence of source data,
18 and then we also recognized that there is a thing as
19 publication bias, you know, positive results get published,
20 many authors are less likely to publish or want to seek
21 publication for a negative result.

22 So, those are just things we were aware of in
23 terms of literature review problems.

24 [Slide.]

25 We do conclude that from looking at these various

1 articles, that there is enough information and enough
2 supportive information to give an intended use of N-13
3 ammonia to assess myocardial perfusion. We find that this
4 is consistent across many studies, long periods of time, in
5 diverse populations.

6 We also feel that the perfusion indication is not
7 limited to the large and medium-size vessels, but also to
8 microperfusion, and we had enough information to have
9 confidence in the performance accuracy of this test.

10 [Slide.]

11 We also were able to get safety information from
12 the published literature. A small amount of ammonia is
13 introduced. We know that the metabolism of ammonia is to
14 urea and to glutamine, and that it is primarily excreted in
15 the urine. There is a short half-life. That was documented
16 in the literature, a short physical half-life, as well as
17 short effective blood half-life.

18 The radiation dosimetry is acceptable, the
19 radiation risk is also acceptable.

20 [Slide.]

21 That is our conclusion for N-13 ammonia.

22 I would be happy to answer any kind of questions
23 you have.

24 **Discussion of PET Ammonia Literature Review**

25 DR. BARRIO: Have you in your assessment analyzed

1 , or decided which are the many conditions for which a
2 perfusion analysis with PET ammonia could be recommended?

3 DR. HOUN: In the literature, there were a variety
4 of conditions, and I think by not limiting specific
5 conditions, because there were so many different things
6 tested, and some of the studies, though, were very limited,
7 so in terms of trying to give each one an indication, we
8 thought the best approach for clinicians would be to have a
9 functional indication of perfusion where you thought a
10 patient needed that type of investigation, that was up to
11 you, and not to say for the diagnosis of a specific entity,
12 because the literature was very varied in what conditions
13 were studied.

14 Some of them were very experimental, but maybe
15 very useful, and we didn't want to really just limit it to
16 specific conditions.

17 What do you think about that approach?

18 DR. BARRIO: We think it is a good approach. We
19 have concerns, however, of the level of reimbursement. I
20 think conceptually and scientifically it is the right thing
21 to do. I think we will agree I guess conceptually that that
22 is the idea, but in terms of reimbursement, sometimes more
23 data may be requested to specifically indicate whether it
24 might be useful here or there, even though it still is a
25 perfusion marker.

1, I don't know if you see my point, but we like to
2 have your support here, if you feel that this is a compound
3 that does the job that it is supposed to do as a perfusion
4 marker, just to also make sure or at least facilitate the
5 process.

6 When we get to the point of reimbursement, that
7 idea is understood and knowing your data would be required
8 to go through a reimbursement process.

9 MS. AXELRAD: I think that we all probably want to
10 comment on this. I think that what we have to do, as Dr.
11 Love suggested, is that we are trying to figure out what we
12 can derive from the literature in terms of demonstrating the
13 safety and efficacy of these compounds for a particular use
14 that would be going on a label.

15 What happens after that in terms of reimbursement
16 and how they are going to slice this down into individual
17 uses is a separate question, and I think that we want to go
18 as far as we can based on the literature with regard to the
19 specific indication, but if you think that you want us to go
20 further, then, I think we need to know exactly what claims
21 you think we would need, and I think that now that we are
22 sharing with you how we are going about this, we would like
23 you to do some of the analysis the way we did that would
24 suggest how something more specific, a more specific claim,
25 for example, would be supported.

1 I mean I wanted to stress how incredibly unusual
2 this is. We sort of alluded to it earlier. Usually, the
3 applicant submits a New Drug Application that analyzes all
4 these different claims that they would like on the label,
5 and we review them and critique them.

6 In this case, we are doing the review ourselves
7 from the literature, and we can only do that to a certain
8 extent. I mean it is taking a very large number of
9 resources in the Agency to do this, and we are doing it, and
10 we are going to try and do it for some of the commonly used
11 drugs and for some of the more commonly used indications.

12 But if we want to get down to the finer points, I
13 think we are going to have to rely on you and know what it
14 is you want, and then perhaps have you do some of these
15 kinds of analyses that we can then review.

16 DR. BARRIO: When I sent you the ammonia
17 literature, I remember -- I don't have it in front of me
18 right now -- but divided in four independent situations, I
19 don't remember specifically what they were, but as a pre-op,
20 follow-up, tests, ammonia control and administration, et
21 cetera, put together by ability and flow, but are just
22 examples.

23 I personally understand and I think most of us
24 will understand what you are trying to do here, and I think
25 it is perfectly fine. I think this is conceptually the

1 right thing to do. We are a little -- well, we should, you
2 are absolutely right. There is a second step, absolutely no
3 question, and the same applies for literature, too. We like
4 to make sure that whatever the proposal is, is something
5 that is understood by the next agency that is going to deal
6 with this issue, and we don't have to initiate a new battle
7 in the process to get this going.

8 DR. LOVE: I think what I am hearing you say is
9 that you would like to see the language in the labeled
10 indication, the approved indication, sufficient to address
11 some of these other questions, so let me just pursue that a
12 little bit in terms of your expected uses.

13 Now, you mentioned rest/stress responses. I think
14 earlier, while motion has been mentioned, infarction, that
15 sort of diagnostic or presence of a diagnosis which may or
16 may not include the use with FDG, and FDG is coming, and
17 also perhaps a pre-op in terms of triaging, which patients
18 may or may not need to go to surgery, or predictive
19 outcomes, something of that sort.

20 I think that part of the indication maybe we can
21 talk about in general because it requires both products
22 perhaps, but let me ask, are you seeking something that
23 would give you specific language in each of these
24 indications meaning it is useful for evaluation of
25 myocardial perfusion, microperfusion, what have you, instead

1 of general approaches or categories?

2 DR. BARRIO: Yes.

3 DR. LOVE: Or in the evaluation, something more
4 general in the evaluation of myocardial disorders or
5 surgical preoperative evaluations?

6 DR. COLEMAN: We have been thinking about
7 something. N-13 ammonia is a myocardial perfusion tracer
8 which is useful in conditions such as suspected or
9 documented coronary artery disease, determine the effect of
10 therapy on coronary artery disease, and with FDG in
11 detecting viable myocardium. Those I just wrote down here
12 as I was thinking.

13 So, that type of thing, I think we are thinking,
14 yes, it is a perfusion tracer, and it is useful in
15 conditions such as.

16 DR. LOVE: The reason I am asking is normally,
17 when we actually get to the labeling -- and we are not at a
18 labeling phase at this moment in time -- but we usually do
19 try to put this functional evaluation in the context of a
20 clinical disorder or group of disorders.

21 So, I would anticipate that there would be some
22 language. We have not actually moved to that point of
23 figuring out exactly what that language would be, and
24 certainly in recognition of the fact that this also has to
25 fit with FDG to some extent, that language would wait until

1 we have both products completed in terms of this part of the
2 language and statement.

3 DR. CONTI: I have a question in terms of
4 precedent. Citing examples is certainly possible
5 particularly in the labeling process, is that correct?

6 DR. LOVE: Citing examples you mean?

7 DR. CONTI: As we just discussed, saying such as
8 certain populations.

9 DR. LOVE: Well, we usually don't use the term
10 "such as" in an indication section. Usually, the indication
11 is relative clear, but it can be broad. We also have a
12 clinical trial section in a label which would give more of
13 the context of the studies and the source of the data that
14 was used to make the final decisions.

15 DR. CONTI: Another question, too. Since we are
16 looking at perfusion per se, there are a number of other
17 perfusion tracers that exist, as well. What is the ability
18 to cross-reference the indications that are used generally,
19 let's say for thallium imaging?

20 DR. LOVE: That is sort of why I was asking the
21 question. Their labeling has a statement that says such
22 things as it is useful in the evaluation of myocardial
23 function. It talks about rest/stress and response either to
24 exercise of pharmacologic stress agents, and the like.

25 So, several of them have different sets of

1, language based on the data that they provided, but as I say,
2 it is usually not a "such as," it is usually a more
3 descriptive --

4 DR. HOUN: It describes where these were studied
5 and that the effectiveness, the performance of the test was
6 accurate in this kind of population, looking at this
7 problem. So, you are right. Right now we just have to
8 assess perfusion, and we have a bunch of studies that are in
9 a lot of different kinds of populations, and the next step
10 is when we do look at labeling, is to be able to make a jump
11 from what the study population would be supportive to
12 describe in this label.

13 In coronary artery disease, like to assess
14 myocardial perfusion, you know, in terms of looking at
15 coronary artery disease, that certainly has been a constant
16 theme in all these articles. So, what other constant themes
17 like we can make that are probably the broader --

18 DR. COLEMAN: The myocardial viability, I think is
19 another one like that, and I think those are going to be the
20 two big ones, is to diagnose and determine the effect of
21 therapy on coronary artery disease and to look at myocardial
22 viability. Those are going to be the big categories here.

23 MS. AXELRAD: Could I just remind everybody to
24 speak up. The people are having trouble hearing.

25 DR. LOVE: But at any rate, as I am saying, all of

1 these different issues come into play when we get to final
2 labeling. Dr. Houn has talked about some of the specific
3 aspects and highlighted certain studies, but there is a
4 total combination of information that is provided, and we
5 would be looking at all of that and coming up with the
6 actual language that would be used.

7 MS. KEPPLER: I don't know if this would be useful
8 right now, but I might throw this out as a possibility, is
9 since we are learning the process, you know, general
10 myocardial perfusion, that is well known, you know, how that
11 would be used, so I think that that is something that people
12 understand, and I guess part of our concerns are, you know,
13 other functional assessments with some of the other tracers
14 are not going to be quite as easily understood how it is
15 going to be used by somebody reading it.

16 I am wondering if it would be useful for us to
17 talk about, you know, just in general terms, what would have
18 needed to have been different in the literature to take it
19 to the next level here, because this is something that is
20 completed and done, and we can look at, and then we can use
21 that knowledge of the evaluation process as we go forward
22 with FDG, you know, which is obviously going to be a little
23 bit more difficult.

24 DR. LOVE: We probably need to talk about FDG
25 perhaps before we get to that, because we do recognize the

1 relationships, and one of the things that Dr. Raczkowski is
2 going to talk about is the myocardial aspects of that, so
3 maybe that can be tabled until we hear this part of the
4 conversation.

5 MS. TESAR: I think that leads us, you know, I
6 think we are coming back to what I asked before is, you
7 know, where do these levels, you know, really affect us, and
8 I think we can talk about that later.

9 I think what we are looking at, as Jane mentioned
10 before, two different processes. We want to get through
11 this process with the FDA, and this is a very comprehensive
12 review. It is very impressive, and thank you.

13 But then, you know, we just don't know. Our other
14 concern is on the HCFA and reimbursement side, and that is
15 our issue that we need to deal with. So, we don't know how
16 they respond to what these levels actually mean, and I think
17 that we are looking at that as one of our primary concerns.

18 DR. COLEMAN: I think on top of that, what we can
19 say about the drug, too, about the radiopharmaceutical, it
20 is my understanding from a commercial standpoint --

21 MS. AXELRAD: That, we will be able to talk about
22 I think. In terms of the process, let me just say a little
23 bit. What we have done today is presented the preliminary
24 results of our review. That review will be documented. It
25 will be a written review, and we will make that available.

1 We also will probably be presenting this to an
2 advisory committee. I don't want to commit to that 100
3 percent, but it is likely that we will present both FDG and
4 ammonia to an advisory committee.

5 That is what we did with the -- the only one that
6 I have been involved with before was the oral contraceptives
7 issue where they added to oral contraceptives labeling or
8 looked at the safety and efficacy of the emergency morning-
9 after use of oral contraceptives, and the Agency did that in
10 response to a citizen's petition, but we looked at the
11 literature.

12 We came to some conclusions, and we presented them
13 to an advisory committee, which the advisory committee
14 endorsed, and that led to a Federal Register notice
15 indicating that we had made some conclusions about the
16 safety and efficacy of that particular indication and
17 encouraged people to submit applications that would add that
18 indication to the labeling.

19 So, we are sort of following the same sort of a
20 model here, where the Agency will make some findings on the
21 safety and efficacy of these drugs for certain indications.
22 We will probably present them to an advisory committee, and
23 then we will publish something that can be used as a safety
24 and efficacy piece of an application.

25 It may go so far as to have labeling in there, so

1 that the entire safety and efficacy part of the application
2 will be these conclusions or citations to the literature and
3 a labeling. But we will have this review, and I think that
4 the review, I think Florence laid out a lot of her thinking,
5 but the review will also I think discuss in a little more
6 detail some of the strengths and the weaknesses of the
7 articles, and so that will sort of illuminate the thinking a
8 little more when you actually see that.

9 DR. COLEMAN: From our standpoint, we are very
10 interested in having this approved as a myocardial perfusion
11 agent, but we are also interested in seeing or having right
12 below that, that the data support its use for pharmacologic
13 stress and assessing the severity of coronary artery
14 disease, and some of these other things that would be not
15 necessarily a "such as," but in the same paragraph, whether
16 it is part of an indication or just how it is done it
17 nebulous to us, but we would like to work with you to come
18 to some agreement based on the literature and its analysis
19 that there would be some specific comments about the
20 indications.

21 MS. AXELRAD: One of the things that I was
22 thinking about, it may be impossible to look at some of the
23 information we have on these other imaging agents, and to
24 the extent that some of that information may be publicly
25 available or could be made publicly available. Since I

1 don't know what is in them, I don't know whether that would
2 help at all, but we could look to see how some of these
3 other claims were documented or made, and our review of them
4 was documented, and we could then see.

5 DR. LOVE: Some of the pieces that you are
6 addressing actually are contained in some of the data that
7 has been identified. I mean the identification of the
8 coronary artery disease, this is in the context of coronary
9 artery disease and the severity, which was the set of data
10 that was presented.

11 There is information on wall motion, and the like.
12 I guess what I am really saying is there is a lot of data
13 here. The extent to which we need additional data may be
14 premature. I think what we really need to do is think about
15 the labeling language that might be reasonable, see the
16 extent to which what you are talking about can be addressed,
17 and then talk from there once we look at it, and if there is
18 something else that we need, maybe there is another article
19 or something else, then, we can point to it at that point,
20 but I think at this moment we have a lot.

21 MS. AXELRAD: I am trying to jump ahead because I
22 am anticipating at some point we are going to say that this
23 is what we can give you, and you are going to want something
24 else. Well, maybe not, maybe not. I am just guessing that
25 that just might be the case.

1 So, what I am trying to figure out is a way for
2 having you to provide whatever it is that we need without us
3 having to go digging for it. That is all I am trying to get
4 at, if we get to that point.

5 DR. COLEMAN: I think as Patricia said, and as
6 Florence pointed out, I mean there is a lot of data here
7 that really, I think, covers the topics that we are
8 interested in having included as part of that indication. I
9 think it just wasn't presented in the wording -- well, it
10 wasn't presented in the wording that I would like to see in
11 indications, but I think it is all there and hopefully we
12 can work with you on that aspect of it.

13 I guess from that standpoint, how would we go
14 forward from this, then, I mean do you need from us the
15 specific areas we would like covered, or how do we move?

16 DR. RACZKOWSKI: Before we actually go into that,
17 let me just comment briefly. We understand your concern.
18 The indications are based on data, and which has been
19 mentioned oftentimes appears in the clinical trial section
20 of the labeling.

21 As Florence had said earlier, a lot of times, you
22 know, one of the goals here is to give a broad indication,
23 such as perfusion, and that might be used wherever a
24 perfusion agent is useful, which is largely the practice of
25 medicine, and there may not be a reason to distinguish one

1 product from another product unless there are some specific
2 advantages or disadvantages choosing one versus the other.

3 DR. COLEMAN: Our concern there is when we get to
4 third-party payers. You know, we are using this to diagnose
5 coronary artery disease, and they will look at the package
6 insert. Well, it says to assess perfusion, it doesn't say
7 to diagnose coronary artery disease, and we are concerned
8 about how that data will be used by other agencies for
9 reimbursement purposes, I mean to be blunt about it, and
10 that is our concern.

11 If we don't have some of the more specific
12 wording, they are going to say, well, the FDA says it
13 assesses perfusion, it doesn't say that it can be used to
14 assess the severity of coronary artery disease. Whereas, if
15 that is in the package insert, that will get us over that
16 hurdle.

17 MS. AXELRAD: Well, we will have to have some
18 discussions. I know that there is a meeting scheduled with
19 HCFA. It is going to be having a meeting on the oncology
20 indications for FDG in January. I think that we will have
21 to have some discussions to make sure that everybody's
22 expectations are being met, I think is the way I would put
23 that.

24 What we will do is talk about where we are going,
25 probably not now, but I think that our next step will be to

1 see how this is going to translate into a label basically,
2 and then have some discussions with you about how we think
3 it will translate, and then go from there to where we go
4 next.

5 DR. CONTI: Jane, I have a question for you about
6 the advisory panel. How do you envision that, is that an
7 external, internal?

8 MS. AXELRAD: It will be an open public meeting,
9 and it will be a real advisory committee meeting. We have a
10 Medical Imaging Advisory Committee meet several times a
11 year. We will put this on the agenda for one of their
12 scheduled meetings.

13 We will make a presentation pretty much like you
14 heard, the public will be invited, and we will solicit their
15 views on it.

16 DR. RACZKOWSKI: And there may be other member
17 from other advisory committees, like in this case, from the
18 Cardiorenal Advisory Committee or, in the case of FDG,
19 someone from the Oncologic Advisory Committee, as well,
20 someone from the specific use side of it.

21 MS. AXELRAD: Usually, we make a presentation and
22 the applicant make a presentation, in this case, I guess, we
23 will make a presentation, and if you want to make a
24 presentation, you could, and then there will be an open
25 public discussion, and then they will tell us whether they

1 endorse this or not.

2 DR. COLEMAN: After the labeling discussions have
3 occurred?

4 MS. AXELRAD: Probably after the labeling. I mean
5 I want to finish -- I don't want to just do ammonia, I want
6 to go with FDG, too, whatever way that comes out, for at
7 least, you know, whatever the indications are that we look
8 at, and so I am envisioning sometime in the spring we would
9 be presenting it to them. I don't think we could probably
10 do it any earlier than the spring.

11 DR. COLEMAN: Probably about seven years ago, we
12 did present FDG to the MIDAC, but oncology applications were
13 not discussed at that time, the neurologic and cardiologic
14 applications were.

15 DR. RACZKOWSKI: But I think we should go back to
16 what you said earlier. I think it would be helpful from our
17 perspective if we knew exactly the "such as," things that
18 you were interested in, if it is for the diagnosis of
19 coronary artery disease or for use in stress testing, having
20 a list of those would be helpful to us.

21 MS. AXELRAD: I think it would be useful for you
22 to look at the labels of products that are out there and
23 actually give us language of what you would want to see in
24 the label, written up the way it will actually look in the
25 label.

1 DR. LOVE: And look at some of the more recent
2 ones.

3 DR. COLEMAN: The wording and looking at the data
4 that would support it. We will get those to you.

5 MS. AXELRAD: I suggest that we take a break. We
6 can continue with this discussion after the break, but why
7 don't we take a 10-minute break.

8 [Recess.]

9 MS. AXELRAD: Before we turn to FDG, does anybody
10 have any other issues or things that they want to talk about
11 on ammonia?

12 [No response.]

13 MS. AXELRAD: Okay, Victor.

14 **Presentation of PET FDG Literature Review**

15 DR. RACZKOWSKI: Florence talked about N-13
16 ammonia, and I will be talking about the FDG review. The
17 focus of my presentation this morning will be on the
18 clinical and statistical literature review. There will be
19 much less emphasis placed on some of the other disciplines,
20 such as chemistry or pharmacology or biopharmaceutics that
21 ordinarily go into a review of any drug product.

22 As I go through this talk, please keep in mind
23 that there are other parts and other disciplines that we
24 usually include in our reviews of drug products. My talk
25 today will really be limited to the cardiac indications for

1, FDG. Our team is running a little bit behind
2 administratively from the ammonia team, and are reviewing
3 the cardiac indications currently.

4 [Slide.]

5 I want to acknowledge the other members of the
6 team: Dr. Sobhan, the statistician, also, I particularly
7 want to acknowledge our program project manager, who is Ruby
8 Jordan, and Kim Colangelo, and R.K. Leedum, because they
9 have done a tremendous amount of work just in terms of
10 helping get some of these literature references, helping
11 track things down, and keeping things organized.

12 The other disciplines are microbiology, David
13 Hussong; R. Kasliwal, the chemist; Dr. Lanionu, who is a
14 pharmacologist/toxicologist; and Alfredo Sancho, who is the
15 biopharmaceutics reviewer.

16 [Slide.]

17 Like Florence, what I would like to do is give you
18 my conclusions at the beginning of the talk or our
19 preliminary conclusions with our review at the beginning of
20 the talk, so you don't wonder where we are heading with
21 this, and from a clinical and statistical perspective, it
22 appears that there is probably sufficient evidence in the
23 literature for FDG to be able to identify "viable"
24 myocardium. I put the word "viable" in quotation marks
25 because that word is sometime used differently by different

1 people, and if you are interested, we could talk about some
2 of the implications of that.

3 In some ways our review was easier than the
4 ammonia review, because we already had a previous NDA that
5 was submitted, and so from the safety perspective we already
6 had dosimetry information for FDG, we already had some
7 clinical safety data on FDG.

8 [Slide.]

9 The search criteria that we used were essentially
10 identical to the search criteria that we used for the
11 ammonia. We wish to thank you for the articles that you
12 submitted. I will be referring to some of those later in
13 the talk.

14 I also want to comment that another source of
15 references for the cardiac indications for FDG came from the
16 American College of Cardiology and the American Heart
17 Association guideline statements that are both in
18 circulation and the Journal of the American College of
19 Cardiology, and from the USPDI and the Society of Nuclear
20 Medicine position statements.

21 [Slide.]

22 This gives you a little bit of an idea of the
23 number of references that were retrieved on the literature
24 search, and these include both references for cardiologic
25 indications and for other indications, such as oncology or

1, neurology.

2 [Slide.]

3 I apologize for the format on the slides, but this
4 represents the conversion, I guess, from Power Point 7 to
5 Power Point 4.

6 When we began our review from the clinical and
7 statistical perspective, one of the things we did is reflect
8 on exactly where we might be going with this, and I think a
9 useful framework for the review is summarized in the draft
10 Medical Imaging guidance, which has already been discussed.

11 As I was talking with Jennifer earlier, it is not
12 that we are implementing that draft guidance for FDG, which
13 there is literature going back for decades now, but I still
14 think that it provides a useful framework in terms for us to
15 talk about a common way to think about how to review and how
16 to approach these products, and it certainly has
17 implications for products that might be developed in the
18 future.

19 [Slide.]

20 As Dr. Love has already alluded to, there are a
21 number of different potential claims that are outlined in
22 that guidance document, ranging from structural delineation
23 and functional, biochemical assessment, all the way up to
24 diagnostic and therapeutic patient management decisions.

25 My purpose for showing this slide is to let you

1 know that when we did the literature review for the cardiac
2 indications for FDG, we approached it with an open mind,
3 thinking about which -- if you had to put it into a box,
4 maybe which box would it go into, although as Dr. Love has
5 alluded to, oftentimes products fit into more than one
6 category, more than one box, and so we are not necessarily
7 limiting things by that, but this provided the framework for
8 our review.

9 DR. COLEMAN: Victor, did you say you have been
10 developing multiple claims, other claims with the last two
11 on that last slide?

12 DR. RACZKOWSKI: The question was did I say
13 something about multiple claims or other claims, and what
14 multiple claims are is that sometimes things cross the line,
15 and for example, you might have -- and I will use the
16 example of ammonia, drugs that might be useful for
17 perfusion, and perhaps might also get a claim for disease or
18 pathology detection or assessment -- in other words, many
19 drugs or many radiopharmaceuticals or many PET products,
20 diagnostic agents in general fit into more than one
21 category.

22 This framework was developed by the Medical
23 Imaging and Drug Advisory Committee, with their assistance
24 with input from the radiopharmaceutical industry, and it was
25 a response in large part by the Agency to try to acknowledge

1, some of the thinking of the diagnostic community.

2 We simply put down multiple claims to acknowledge
3 that sometimes don't neatly fit into one box, they may
4 straddle more than one box, other claims or things that may
5 not be encompassed by the above, and I can't think of a
6 specific example right now, but the basic recommendation in
7 the guidance document is that if you are ever in that
8 situation, just to approach the Agency and have some
9 discussions prior to doing some of the clinical trials with
10 it.

11 DR. CONTI: This sort of overlaps back to the
12 ammonia conversation we had a few moments ago, and to pick
13 up a little bit on what Dr. Coleman just said.

14 Is it your intention to, if we are going to follow
15 this draft guidance for the medical imaging drugs and
16 biologics, is it your intention to try to assign, first,
17 functional physiological or biochemical assessment, and then
18 deal with issues that are more disease-specific, or does it
19 matter?

20 DR. RACZKOWSKI: I think the answer to that
21 question is no, at least the way we approached this data
22 set. The idea was to look in terms of what the literature
23 actually had in terms of data, in terms of clinical trials,
24 and get an idea of what the actual use patterns were and to
25 see what sort of claims might come from that.

1 MS. AXELRAD: The guidance is really designed for
2 applicants who are putting together New Drug Applications,
3 and to guide them in how to design their clinical trials in
4 a way that will provide the necessary information to support
5 the various levels of claims.

6 Here, we are doing it backwards in that we are
7 trying to look at the literature and to see what claim could
8 be made by it, and, in fact, really without knowing exactly
9 from you what claim you wanted to make.

10 So, we were trying to look at it and just see what
11 is the best we think we can do here, and I think that on the
12 ammonia discussion, you know, we said this is where we came
13 out sort of relatively easily, if we want more detail, we
14 need to have some further discussions about that.

15 We might want to have some of the discussions
16 about the oncology indications earlier, so that when we are
17 looking through the literature, we can be guided by what you
18 are really looking for in terms of a claim.

19 DR. RACZKOWSKI: My intent for showing this slide
20 was because I think it just provides a common framework that
21 we can talk about. It is not that we are necessarily try to
22 squeeze something into a particular box.

23 [Slide.]

24 Some of the things that we Medical Image guidance
25 document does stress, that whatever an imaging agent does or

1, PET product does, is that the information that is provided
2 by that has to be valid.

3 What valid means in this context is simply that
4 the drug is doing what it says it does, and then also things
5 about the potential clinical usefulness of the imaging
6 agent.

7 [Slide.]

8 Just as Florence outlined a number of things that
9 the ammonia team was looking at in their review, in a
10 clinical and statistical review of the FDG products, there
11 were some very similar concerns in terms of details of study
12 design, study population, how images were actually acquired
13 or interpreted, statistical analyses, and so forth, whether
14 the study population was sufficiently similar to the
15 population that might ultimately receive the imaging agent,
16 and whether procedures were followed to reduce potential
17 bias in the clinical trials.

18 I will go into some specific examples of this when
19 I talk about specific literature articles, just to give you
20 a better flavor of what our thinking might be.

21 [Slide.]

22 Based on a number of criteria which I have
23 outlined, our initial literature selection boiled down to
24 roughly 10 or 11 articles that appeared to support a claim
25 for FDG for myocardial viability, and I have put asterisks

1, by some of those that were provided by the PET community.
2 Again, I will be going through some of these specific
3 examples.

4 [Slide.]

5 But at this point I think it is worth just
6 mentioning some of the inherent issues about literature
7 review. This is much like putting together a jigsaw puzzle,
8 you know, it is hard to find definitive literature article,
9 so what I thought I would do is give a sampling of some of
10 the thinking about four or five of the literature articles
11 that we have review that we think help support a viability
12 claim for FDG.

13 My intent in talking about the strength and
14 weaknesses of those articles is not to single out particular
15 articles or single out particular authors, in fact, I would
16 take some risk at doing that, but rather, it is to give you
17 a more concrete idea of some of the issues we face when we
18 actually look at the literature.

19 MS. AXELRAD: None of the authors are in the room,
20 I hope.

21 [Laughter.]

22 DR. RACZKOWSKI: The next set of slides and
23 through most of the remainder of this talk, I will be
24 talking about four or five different clinical trials. Like
25 Florence, I have outlined them in the way we traditionally

1 think about these sorts of things, because the ultimate goal
2 is to provide labeling for a product.

3 [Slide.]

4 The first study I will talk about is by Carrel, et
5 al., and the objective of the study was to assess systolic
6 and diastolic left ventricular function after coronary
7 artery bypass grafting surgery.

8 One thing that is common to many of these trials
9 is they are all very similar in their design, and most of
10 them had some sort of PET imaging, both for perfusion and
11 FDG for viability, done prior, an assessment of myocardial
12 function done prior to some sort of intervention, such as
13 CABG, and then there was some sort of follow-up done
14 afterwards in terms of myocardial function or in terms of
15 clinical outcomes.

16 So, in this particular study, rubidium was used as
17 an agent to evaluate perfusion, and FDG was used to evaluate
18 myocardial perfusion. Two-dimensional echocardiography was
19 done both prior to and after CABG in order to assess
20 myocardial function.

21 The functions that were evaluated, the endpoints
22 on that slide, like left ventricular ejection fraction, both
23 global and regional wall motion, diastolic relaxation, the
24 New York Heart Association functional class.

25 There were 23 subjects with coronary artery

1 disease who were enrolled. All had left ventricular
2 ejection fraction less than 45 percent before CABG.

3 One of the comments that I will make about this
4 particular article is that in the image evaluations, the
5 section of the materials and methods part of the article is
6 that it didn't really specify whether the PET or two-
7 dimensional echo readings were blinded, and by "blinded," we
8 usually mean to one another, in other words, you don't want
9 the PET images to influence somebody's interpretation of
10 ventricular function, and conversely, you don't want
11 someone's interpretation of a 2-D echocardiogram to
12 influence his or her reading of the PET images.

13 Oftentimes that implies a lack of familiarity with
14 the clinical course of the subject, as well. That is the
15 sense in which we use the term "blinded."

16 MS. AXELRAD: We might want to talk about that
17 concept later, after you get through, and we might want to
18 talk about -- I mean I don't know if it would be useful or
19 even necessary to get information, and to the extent in some
20 of these articles there are things missing, it might be
21 possible to get some of that information on these things,
22 and we might talk about whether it would be useful for some
23 of these points that you find particular important as to
24 whether it would be worth trying to get that information.

25 But also I want people to take away that it would

1, be really useful for new stuff, that if you are doing
2 studies for new compounds or new indications, that we have
3 this have this kind of information.

4 [Slide.]

5 DR. RACZKOWSKI: So, the results of that study
6 again, looking at the primary endpoints, left ventricular
7 ejection fraction was significantly increased both at rest
8 and at exercise. Wall motion, there was no overall change
9 in segmental wall motion score before and after CABG
10 surgery, however, if you looked at the predictive value of
11 FDG to predict functional improvement, there was 84 percent
12 of the segments read, the so-called mismatch pattern in
13 which you have increased uptake of FDG and normal or
14 decreased perfusion to a particular myocardial segment,
15 there was an 84 percent prediction rate there, which usually
16 indicates some sort of injured, but not irreversibly injured
17 myocardial segment.

18 Conversely, there were only a few number of
19 segments that were evaluated, and so the confidence
20 intervals are very broad here, but there was only 25 percent
21 improvement, functional improvement, in those with the match
22 pattern, which oftentimes implies some sort of irreversible
23 injury.

24 I will just comment here because this is one of
25 the few papers that I have cited that actually looked at

1, this, but some of the clinical outcomes were actually
2 evaluated, and just as a general statement, the New York
3 Heart Association class improved for nearly all patients.

4 [Slide.]

5 Some of the strengths of this protocol was that it
6 specifically was prospective, and it is difficult to
7 sometimes figure that out from reading the literature, but
8 this one actually indicated that it was a prospective study.

9 As I indicated, it evaluated a whole spectrum of
10 outcomes, not only regional left ventricular function,
11 meaning the particular myocardial segments or regions of the
12 myocardium, but also global left ventricular function, such
13 as ejection fraction, and then carrying that one step
14 further and looking at clinical outcomes, such as New York
15 Heart Association functional classification.

16 Another useful thing about this article was that
17 some of the endpoints were evaluated at more than one time
18 point afterwards. For example, myocardial function with
19 echocardiography was not just evaluated at one time point,
20 which is I would say usually what I have seen in most of the
21 articles, but there were a couple time points evaluated, and
22 that sort of information is very helpful in terms of having
23 longitudinal data about what might be optimal times for
24 evaluating something.

25 Also, the graft patency was assessed

1, postoperatively.

2 [Slide.]

3 Some of the weaknesses were small sample size. We
4 see that a lot in many of these articles. Again, that is
5 why I think when there is, this is somewhat like a jigsaw
6 puzzle, seeing where the preponderance of the data for many
7 different small articles actually, with small sample sizes
8 support a claim.

9 It didn't say, but probably in the lack of it
10 saying, probably the PET and two-dimensional
11 echocardiography images were not read blindly. Some of the
12 data was really left out in the evaluation. Only one
13 myocardial segment was evaluated in each patient, and again
14 there were only 20 or so patients in the study, and so
15 rather than looking at all the myocardial segments from all
16 the patients, or at least all the dysfunctional myocardial
17 segments from all the patients, or all those with mismatch
18 and all those with match, this selected some of the
19 segments, and we like to see an overall assessment, because
20 there is always some sort of bias in selecting segments, and
21 that could influence the results and conclusions that come
22 from the trial.

23 Another thing that we are starting to see a lot of
24 is we have two different technologies here or two different
25 modalities, two-dimensional echocardiography, trying to get

1, a common -- when you are talking about myocardial segments,
2 trying to align the planes of imaging in such a way that
3 you are actually sure that you are talking about the same
4 segment of myocardium, and in this particular article, it
5 was unclear how or whether that was done at all.

6 DR. COLEMAN: Victor, that is a big problem we all
7 have. I wish there was a good answer for that one, but you
8 have just got to work and really stress how you do it, I
9 think it certainly should be included how one has tried to
10 relate those.

11 DR. RACZKOWSKI: And I think that some of the
12 subsequent papers, you will see that some of the authors
13 actually did do that.

14 DR. COLEMAN: It is not easy regardless.

15 DR. RACZKOWSKI: Right absolutely.

16 [Slide.]

17 It was difficult to find some very basic
18 information in this manuscript about some very fundamental
19 things about what dose of FDG was actually used, how many
20 millicuries or what the PET protocol was for imaging.

21 There was a reference that was supplied in the
22 manuscript, but it was a reference in German that was not
23 readily available to us.

24 [Slide.]

25 The second study I would like to comment on is the

1, study by Marwick, et al., and the objective of this study
2 was to evaluate the metabolic response of hibernating tissue
3 to revascularization, and for those in the room who may not
4 be familiar with this particular area, hibernating
5 myocardium is a term that is used to describe myocardial
6 tissue that still has not lost its function, but is
7 dysfunctional due to some sort of chronic insult, usually a
8 lack of perfusion.

9 The design was similar to the others. There was
10 both pre- and post-assessments, in this case, though, of
11 perfusion with rubidium, and also used two-dimensional
12 echocardiography to evaluate functional outcomes, and the
13 functional outcomes that were evaluated were wall motion
14 with echocardiography, rubidium was used to evaluate
15 perfusion, and FDG activity, since they did PET studies both
16 before and after CABG, this is one of the few studies that
17 actually did that, assessments could be made both of
18 perfusion and of FDG activity both pre- and post-surgical
19 intervention.

20 Again, it was a small trial, only 16 patients.
21 They were fasting. Again, those are the sorts of details,
22 particularly with something like FDG, whether a patient is
23 fasting or not, or whether the patient is glucose loaded or
24 not, that are important to know, because they help us write
25 our instructions for use when we write a package insert, you

1, know, what is the optimal conditions to use the drug under,
2 should it be glucose loaded or fasted or what. So, those
3 sort of details are useful in manuscripts.

4 The severity of the disease was somewhat limited
5 in that there were patients without three-vessel disease,
6 and most of the studies did, this looked both at not only
7 the number of patients, but also the number of segments, and
8 it did have some blinded readers both for the
9 echocardiography and for the PET studies.

10 [Slide.]

11 Basically, the results were there were 85 segments
12 identified with fixed perfusion defects and resting wall
13 motion disturbances, of which 41 percent were classified as
14 hibernating. This specification occurred postoperatively,
15 in other words, the author has looked to see whether
16 function returned, and then if function did return, those
17 segments were classified as being hibernating, if they
18 didn't, they were classified as non-hibernating.

19 [Slide.]

20 But among the hibernating segments, there was a
21 significant improvement in wall motion, an increase in
22 perfusion, and decrease in FDG activity, all things which
23 you would expect if there is some sort of functional
24 recovery and if FDG is really a marker for viability and if
25 it is being trapped in the myocardial cells because of a

1, transfer of metabolic activity from lipid uptake, which is
2 normal myocardial route to glucose uptake.

3 [Slide.]

4 As in many of these studies, those that were
5 classified as being viable versus non-viable, or hibernating
6 versus non-hibernating, there were reciprocal type of
7 results seen in terms of what you would expect, and that the
8 non-hibernating segments, those are the ones that were
9 irreversibly injured, there was a significant percentage of
10 those, 76 percent were correctly predicted to be non-viable
11 by FDG criteria.

12 [Slide.]

13 Again, some of the strengths. Blinded image
14 evaluations both for the PET and for the FDG evaluations --
15 I am sorry -- for the echo evaluations. PET was performed
16 both pre-operative and post-operatively, and here, there was
17 a lot of discussion in this particular article about image
18 alignment.

19 In this case, rubidium was being aligned with the
20 FDG scans, but they talked about how that was done, and it
21 was particularly important in this particular case because
22 this was done under fasting circumstances, and so the
23 rubidium scans provided a useful reference for the FDG
24 images, but also how to align two different modalities,
25 here, echocardiography with PET, and the author has

1, described how they define segment of myocardium both in PET
2 and in echocardiography that were thought to be comparable
3 to one another.

4 [Slide.]

5 Again, small sample size, and some of the sickest
6 patients were excluded from the protocol. Particularly for
7 some of the functional claims, we like to see a broad
8 diversity, a broad range of patients that are being
9 evaluated. We don't only want to see the least sick
10 patients or the most sick patients. We want to have an idea
11 of how the product performs across the entire spectrum of
12 disease severity.

13 [Slide.]

14 The third paper I will talk about is by Tamaki, et
15 al. Its objective was to assess the clinical value of PET
16 in the evaluation of pulmonary artery bypass grafting. In
17 this case, instead of doing echocardiography for functional
18 assessment, radionuclide ventriculography was done both pre-
19 and post-CABG. The endpoints that were evaluated with that
20 were wall motion and perfusion.

21 Again, 22 subjects, relatively small trial,
22 fasting, all of them were undergoing CABG.

23 The image evaluations were done by blinded readers
24 for the PET and again blinded readers for the radionuclide
25 ventriculograms for function, so that is a good thing.

1, [Slide.]

2 Again, I won't spend a lot of time talking about
3 the results, but simply comment that the directions and the
4 sorts of things that were being predicted by the FDG and PET
5 in terms of viability and non-viability of particular
6 segments of myocardium were found in this particular trial,
7 both for wall motion.

8 [Slide.]

9 I think this is less important perhaps for this
10 particular claim, although it does provide some proof of
11 concept for a viability type of claim, is that these authors
12 actually did PET scans after the bypass procedure, and so
13 you can look and see whether those segments that were viable
14 pre-operatively with restoration of perfusion to that
15 myocardial segment, whether or not the FDG changes were, in
16 terms of uptake in that segment, were concordant with what
17 you would expect, in other words, they go down. The same
18 thing is true for the rubidium perfusion.

19 [Slide.]

20 Strengths. There were multiple blinded readers,
21 there was more than one, there were three. Again, PET scans
22 were performed both before and after CABG, and multiple
23 readers, not only for the radionuclide scans, but also for
24 the PET scans.

25 I may have some contradictory things here. Here,

1 I say that the readers of the PET scans were not blinded. I
2 can't recall if that is different from what I have said
3 earlier or not.

4 DR. COLEMAN: You said not blinded.

5 DR. RACZKOWSKI: Thank you.

6 [Slide.]

7 The final study that I want to talk about in terms
8 of the manuscripts, and again these are just for
9 illustrative purposes, so you have an idea of how we
10 approached the literature, is a study by Tillisch, et al.,
11 in the New England Journal of Medicine.

12 A fairly small study, but it was I think one of
13 the first studies, significant studies or most significant
14 studies at a fairly early time.

15 The objective of the study was to determine if FDG
16 in segments without normal motion indicates viability or
17 not, and whether or not it predicts functional recovery.

18 Ammonia was used as a perfusion agent, and FDG was
19 used to assess viability, and both contrast or radionuclide
20 ventriculography depending on the particular patient were
21 used both pre- and post-CABG to assess ventricular function.

22 One of the interesting aspects of this particular
23 article is that a subset of the patients received thallium
24 scanning, so this gets at the issue of some of the
25 comparative types of information that you might be able to

1, get from comparing two different agents to one another, in
2 this case comparing how thallium assesses viability compared
3 to how FDG might be able to assess viability.

4 Seventeen patients. The patients were glucose
5 loaded, 73 segments with abnormal motion were assessed.

6 [Slide.]

7 The dose was 10 mCi of FDG. Endpoints were wall
8 motion and ejection fraction. Blinded readers were used for
9 the contrast and radionuclide ventriculograms.

10 The PET images were evaluated quantitatively, so
11 that doesn't require a reader per se unless you have to go
12 out a region of interest, but in those situations where a
13 region of interest is drawn, we would recommend that those
14 people who are doing that sort of thing be blinded to the
15 results of the other's diagnostic modalities and to the
16 clinical status of the patient.

17 Again, they talked about how regional concordance
18 was achieved between the different types of scans, the
19 radionuclide ventriculography and the PET images.

20 [Slide.]

21 Again, I won't dwell on the results, but to
22 comment that they were basically in the direction that you
23 would expect to see if FDG is able to detect myocardial
24 viability.

25 [Slide.]

1, Many of these strengths and weaknesses I have
2 touched on already - blinded image evaluations. As I have
3 mentioned, this had a quantitative evaluation of PET images
4 and may be less prone to possible biases that are introduced
5 by visual analysis.

6 [Slide.]

7 Again, as part of a proof of concept thing, this
8 study tried to indicate whether revascularization was
9 actually successful or not, because you would expect that if
10 a particular myocardial segment was revascularized, then,
11 you should see changes in that myocardial segment that are
12 concordant with what you would expect for FDG if it is a
13 good marker for viability, and if it is not successful at
14 revascularizing them, not necessarily looking for those
15 sorts of outcomes.

16 [Slide.]

17 That is my summary of just a sampling of some of
18 the articles that we have looked at and what we were
19 thinking about when we review these articles, and I thought
20 I would just shift gears, right here, just to comment
21 briefly on an abstract that appeared in Heart in 1996.

22 It was just an abstract, but I think it is worth
23 commenting on because it raises a number of interesting
24 things, a number of interesting issues. This was done by a
25 cooperative European PET group, so it was done by multiple

1, PET centers in Europe, and this was an interim analysis of
2 some of the results.

3 [Slide.]

4 If you look at just the numbers that were achieved
5 in this sort of trial, 502 patients were enrolled, and at
6 the time of the interim analysis, at the time this abstract
7 appeared, 105 patients had already been completely
8 evaluated. It shows you the type of power that you can get
9 from a multicenter study.

10 Like many of the studies that I have talked about
11 in more detail, it had very similar objectives, and unless
12 the published manuscript, final manuscript comes out before
13 our review is done, because it is an abstract, it won't
14 likely play much in our way of thinking about FDG.

15 But I really wanted to note that the design
16 features that are inherent with some multicenter trials,
17 that when you do multicenter trials, you have a common
18 protocol that multiple investigators are working from, and
19 so almost by definition many times that means it is a
20 prospective study, which is a desirable feature in terms of
21 whether we feel that a particular trial is hypothesis-
22 generating versus confirming a hypothesis.

23 It is a difference between data dredging to try to
24 find something versus saying something upfront about a
25 hypothesis and then confirming it.

1, The other aspect about multicenter trials is that
2 you get probably more generalizability of the results
3 because the patients represent a broader spectrum of
4 patients who you might otherwise see. Particular
5 institutions may have particular peculiarities about the
6 nature of the patients that they see or different
7 peculiarities about the way PET procedures are done, and
8 having a multicenter trial makes it more likely that the
9 results will be robust across different types of patient
10 groups, as well as different types of investigators, and
11 they are not so much dependent on one investigator, so that
12 is a very desirable feature.

13 I really just put this up because I think that
14 this is something perhaps that should be considered in this
15 country for future types of PET products or indications for
16 existing PET products that might be developed.

17 [Slide.]

18 So, just a summary of some of the things I have
19 talked about today. I really want to emphasize that with
20 PET, there was a prior NDA, we know a lot about the basic
21 pharmacology of FDG both from the prior FDG review for the
22 prior NDA, as well as for the current review that was done
23 by Dr. Lanionu in terms of how FDG behaves in the heart and
24 glucose metabolism in the heart vis-a-vis lipid metabolism.

25 Although there were dosimetry data in the original

1, NDA, some of the questions that are raised by our
2 pharmacokinetic or by pharmaceuticals reviewers have to do
3 with what will this product be like when it is used in a
4 widespread population, and do we have any information in
5 diabetic patients not particularly relevant to FDG, whether
6 the patients renally impaired, since it is largely excreted
7 by renal route.

8 So, I think from the efficacy perspective, our
9 preliminary conclusions are that FDG may identify viable
10 myocardium, and from the safety perspective, we had
11 preexisting data from an NDA, which again cited literature
12 articles, but the question we would raise here is, is there
13 any reason to believe that cardiac patients, this particular
14 patient population, might be different than the patient
15 population that was reviewed in that NDA, and that NDA
16 actually did include some cardiac patients even though the
17 indication was for neurological indication.

18 But that is the way we think, and the other issue
19 which was mentioned earlier by I think it was by Dr. Coleman
20 and Dr. Conti, had to do with the safety of these products,
21 and are fairly empirical about the way we think about
22 safety. We like to see concrete data in terms of either
23 animal studies and supplemented with some sort of human
24 data.

25 Usually, safety isn't even mentioned even in

1, passing in many of the journal articles that we read, and so
2 it is unclear if it was really assessed in any way at all or
3 what sort of safety assessments were done.

4 Oftentimes individual investigators might ascribe
5 an adverse event to some sort of underlying disease process,
6 and many of these cardiac patients are very sick, so they
7 might not be ascribed to the drug, but it is only through a
8 really systematic evaluation of safety data and getting some
9 empirical data that we really feel comfortable with reaching
10 the conclusion that a particular drug product is safe.

11 I will stop there.

12 **Discussion of PET FDG Literature Review**

13 MR. SARVI: With regard to the safety data, do you
14 have information about the Silverstein --

15 DR. COLEMAN: Ted Silverstein --

16 MR. SARVI: Ted Silverstein, yes.

17 DR. COLEMAN: -- who heads the USP Committee for
18 the Society of Nuclear Medicine, has kept a running
19 tabulation of number of FDG injections and adverse events.
20 He published that in abstract form, I think about a year
21 ago. He has a manuscript that has been accepted by the
22 Journal of Nuclear Medicine. Do you know when that is
23 coming out? I think that it was 50,000 injections of FDG.

24 MR. SARVI: It was something like 35,000, but it
25 was in the paper more than that.

1, DR. COLEMAN: I think that was discussed actually
2 at one of our conferences. So, that data we will have
3 available for you. Ted said that he would be happy to
4 supply it, and we just haven't followed through on that, but
5 it should be in the peer-reviewed literature in the next few
6 journals at least.

7 DR. CONTI: A comment on the dosimetry and the
8 pharmacokinetic data in the diabetics or renally impaired,
9 have you looked at calculations to, let's say, project if
10 none of the dose was excreted in the perfectly renally
11 impaired person that has not ability to excrete the tracer
12 through the kidneys, what those calculations would be and
13 what kind of level of comfort you have with regard to the
14 dose of the pharmaceutical and taking that into
15 consideration?

16 MR. LEE: David Lee, team leader. As far as I
17 know, I do not have any information as far as dosimetry in
18 renally impaired or hepatically-impaired patients. We do
19 have means to speculate what is going to happen, but that
20 exercise has not been done yet.

21 DR. CONTI: I think that is very important,
22 because if you do your calculations, you will know what your
23 upper limit is going to be with all the dose being
24 maintained and only excreted by the physical half-life of
25 the pharmaceutical, and then you can go from there because

1, if that is acceptable, then, there is no need to do this
2 other exercise.

3 MR. LEE: Right, but one thing for sure, I just
4 wanted to state this upfront, that the literature data we
5 have looked at, we haven't found any dosimetry information
6 in renally or hepatically-impaired patients.

7 DR. CONTI: Maybe the reason is maybe because we
8 have already done those calculations, and from a dosimetry
9 point of view, it is not a problem because of the short
10 half-life of the isotope.

11 I am not dealing with the pharmacology or
12 pharmacokinetics. That is a different issue. I am just
13 talking about the dosimetry vis-a-vis the safety aspect of
14 it.

15 DR. COLEMAN: I don't know of any data either on
16 renal or hepatic insufficiency patients. I don't think that
17 there has been any publications on that.

18 DR. CONTI: There are some guidelines actually in
19 MIRD, I think, with other radiopharmaceuticals that deal
20 with these issues as to how to address those types of
21 conditions in patients with technetium and other isotopes.
22 So, I think that exploring that would be a useful exercise.

23 DR. COLEMAN: Jane, you brought up an issue early
24 on about blinded readings, and importance for clinical
25 studies. I think it is important to do that, to get the

1, idea of these studies, what information is in them, by
2 themselves.

3 But I have discussions with my clinicians, and
4 they don't like that. They like to have how you interpreted
5 them at the time with whatever information you had, that is
6 the information they operate on, which is different than
7 evaluating the technology itself, so it is sort of an
8 interesting way to look at this, but I think that from the
9 utility of the procedure that we are talking about here,
10 having it read blindly would be very important.

11 Most of these I think are going to be read that
12 way, certainly separate from the echo, just knowing the
13 groups and who does what. In very few places does the same
14 person read the PET scans, do the echo. So, just on that
15 basis, they are probably read blindly, but you would need to
16 find that out.

17 I am sure if you communicate with these people,
18 they will say yes or no, and there is no reason to hide it,
19 and there would be no reason to say one way or the other.
20 It is just information.

21 DR. RACZKOWSKI: We recognize that there is
22 differences between what is done on clinical trials in terms
23 of the way images are read versus what might be done in
24 clinical use, and certainly there is nothing to prevent
25 people from doing it both ways. In fact, oftentimes we

1 encourage that because then you have a clear idea of the
2 actual effect of the radiopharmaceutical in an environment
3 where really all you are looking at is the image with
4 minimal information.

5 And then you have the corresponding set of
6 information that corresponds more to the real use and what
7 somebody might use it in, in actual practice, might be.

8 DR. COLEMAN: Another use of FDG in cardiac
9 imaging these days is the so-called DISA protocol that is
10 being used in some institutions, I don't know how many, in
11 the United States, where they do a resting FDG study and a
12 stress sestamibi study to use the resting FDG study as a
13 baseline resting perfusion, if you will, as well as a
14 viability type of tracer.

15 Did you look at any of those studies and do
16 anything with that?

17 DR. RACZKOWSKI: Not in any detail. The real
18 focus of the review was first just to try to figure out
19 where the bulk of the evidence was and how the product is
20 most widely being used, and then trying to select the
21 articles that best supported that. In this case, it was
22 myocardial viability.

23 DR. COLEMAN: But I wonder if we shouldn't think
24 about its use with DISA, looking at resting myocardium -- I
25 am not quite sure what to describe -- it is looking at the

1, glucose accumulation in the resting myocardium for
2 comparison with the stress perfusion information. It
3 certainly is catching on in several institutions now, and I
4 don't know what the fellow panel members think, but it is
5 certainly something that should be discussed.

6 MS. AXELRAD: Excuse my ignorance, but could you
7 tell me what DISA is?

8 DR. COLEMAN: It stands for dual isotope
9 subtraction, I think. I forget the "A" -- acquisition, dual
10 isotope subtraction acquisition study. Instead of doing a
11 rest/stress mibi study, or rest/stress redistribution
12 thallium, they inject the FDG at rest, then, they stress the
13 patient -- they don't image FDG by itself -- then, they
14 inject the sestamibi during stress using exercise stress,
15 and then they do one image, one on the sestamibi photo peak
16 and one on the 511 KEV photo peak.

17 This is done with collimated SPECT imaging is how
18 they do these, and thus, they can use this for diagnosis of
19 coronary artery disease and for determination of myocardial
20 viability. So, it is being used in several institutions now
21 for those indications.

22 DR. BARRIO: You could supposedly do the same
23 thing with stress ammonia.

24 MS. AXELRAD: Is this being done under research or
25 clinically?

1 DR. COLEMAN: Several institutions are doing it
2 clinically now. They have been doing it for several years,
3 and it has become the procedure of choice I know at least in
4 one institution in the United States, it is their standard
5 nuclear cardiology procedure.

6 DR. RACZKOWSKI: The whole issue about modifying
7 SPECT apparatus to detect that high energy photon, it is a
8 very interesting one, and actually, I do have several
9 articles that do talk about that. I was approaching this
10 primarily from the perspective of drug effect as opposed to
11 the device effect.

12 DR. COLEMAN: Right, and I think that is the way
13 we would like to leave it. I think that is the right way to
14 go. I think that just again in the wording, we would want
15 to see how the final wording was to see if that would be an
16 appropriate use of FDG under that circumstance.

17 DR. RACZKOWSKI: There is a potential issue here
18 with whether the image resolution is as good, and so forth,
19 with the SPECT as opposed to the PET imaging, and those
20 sorts of things actually could have an impact on the
21 ultimate performance of the FDG in any particular patient,
22 and so that is something we will probably be thinking about
23 as well.

24 DR. LOVE: You mentioned wording. Earlier, we
25 talked about the ammonia relationships and issues with

1, viability, and now Vic Raczkowski is indicating his
2 conclusions. Are there some general issues that you still
3 have in terms of wording? Are you looking at stress and
4 rest, viability, and we were mentioning earlier viability,
5 and Victor has alluded to the fact --

6 DR. BARRIO: I am talking about what is done in
7 terms of stress is the flow portion. What the flow portion
8 does is tried to make the defect much more visible. Then
9 the rest, FDG will, of course, indicate probably, I think
10 most certainly, the anaerobic utilization of glucose under
11 an oxygen-limiting situation in the impaired myocardial
12 tissue that is still alive or viable.

13 I think that concept is a very powerful
14 utilization of FDG because it gives a positive signal for
15 the defect, metabolic defect. I think this is conceptually
16 analogous to the increased signal in epilepsy observed with
17 FDG that is probably due, at least animal studies may
18 suggest that, to, again, the anaerobic use of FDG during the
19 epileptic seizure.

20 It is something that it is important.
21 Conceptually, you can also look at that effect in a
22 different way, already low utilization of the fatty acid.
23 But it is always much more interesting diagnostically to
24 have a tracer that gives you a positive signal.

25 I think that is also very valuable in the

1, utilization of FDG for this use.

2 DR. RACZKOWSKI: What is your feeling about, for
3 the cardiac indications, the way the community is going in
4 terms of having patients glucose loaded ahead of time versus
5 fasting, or are they euglycemic, or is there a direction
6 that you think people are moving in?

7 DR. BARRIO: I am sorry, about the preparation of
8 the patient for this type of study?

9 DR. RACZKOWSKI: Which way is the community going,
10 is it towards glucose loading, fasting, euglycemic?

11 DR. COLEMAN: It is moving towards glucose loading
12 and/or the euglycemic, hyperinsulinemic clamp, so there are
13 protocols both ways, having patients glucose loaded,
14 checking their glucose levels, and they may or may not get
15 insulin depending on what their glucose level is before they
16 inject the FDG, or just starting with an insulin infusion,
17 insulin glucose infusion to get a fixed level, so both
18 protocols are used rather widely, and I don't know that
19 there is one being preferred over another one right now.

20 MS. TESAR: I think out in the community they
21 don't do the insulin loading as much. I mean I think is
22 more looking at the sugar level at the time, and doing
23 glucose loading and then checking sugar levels.

24 DR. RACZKOWSKI: Actually, there are very few
25 articles, at least that I have found that actually go into

1, the details about how images might be optimized with
2 different glyceimic states.

3 DR. BARRIO: More recent studies are addressing
4 this issue.

5 DR. COLEMAN: There is a little bit on that, you
6 are right, but there is not a whole lot.

7 DR. RACZKOWSKI: Again, I am thinking about the
8 ultimate labeling in terms of what sort of advice would be
9 given in terms of how the product should be given. That
10 sort of information is very helpful.

11 DR. COLEMAN: I agree, I think it is going to have
12 to be in there, and my guess is that there will be a couple
13 of -- you know, depending on what indications we come up
14 with -- but a couple of suggested or a couple of literature
15 ways that have been done to have the glucose level at a
16 certain level when the FDG is injected.

17 One thing again related to that, almost all of the
18 data in the literature has been a combination of FDG and a
19 myocardial perfusion tracer. Some have been N-13 ammonia,
20 some have been rubidium-82, some have been sestamibi or one
21 of the technetium single photon emitters.

22 So, I would think that in the indication and
23 package insert, you would probably want to have it combined
24 with a myocardial perfusion tracer, and not just have it
25 alone as a viability tracer. We were talking about with

1 ammonia.

2 DR. RACZKOWSKI: I am not sure we are really at
3 that point yet. We may simply describe in the clinical
4 trial section what types of perfusion agents were used
5 rather than coming out and specifically recommending one
6 versus another.

7 DR. CONTI: The data basically that you reviewed
8 always uses a resting perfusion agent. I think that is the
9 point, to determine viability, so no matter how you shake it
10 out, you have got to deal with a resting perfusion scan in
11 order to meet criteria that are proposed here.

12 Now, whether it means doing an N-13 ammonia or a
13 resting thallium scan or resting mibi scan or whatever you
14 do, you may want to leave that open-ended for the
15 investigator to choose.

16 DR. RACZKOWSKI: Your point is well understood. I
17 guess I was making a more technical point about whether that
18 would appear in the indication or whether that might appear
19 somewhere else.

20 DR. CONTI: The claim of viability, it is just an
21 issue of what the claim is based on, and the claim is based
22 on a resting perfusion scan with an FDG study.

23 DR. COLEMAN: There has actually been a couple of
24 studies, Victor, you didn't go through those today, but I
25 think mainly from Italy, where they just did FDG alone and

1 did the prediction without the combined perfusion, but I
2 don't know that anybody does that --

3 DR. RACZKOWSKI: I looked at some of those, but
4 felt that there was -- there has been so much, and since we
5 are moving in that direction --

6 DR. COLEMAN: I agree with that, but I think that
7 this just means that this needs to be described in this way
8 now.

9 MS. AXELRAD: I think we are sort of at crossroads
10 here, and we have to choose whether we want to keep going
11 and finish. I mean we don't have anything else to present,
12 and we are sort of here now, that we can talk about next
13 steps and if we want to get into some of the questions about
14 the rule and the guidance, we can do that, or we can break
15 for lunch and come back.

16 DR. CONTI: I thought it might be worthwhile to
17 talk a little bit about the oncology application, have an
18 open-ended discussion about that. In the next meeting, it
19 may make it a little bit easier as far as the presentation.
20 I would suggest that maybe we break for lunch and come back
21 and do that.

22 DR. COLEMAN: I think so, too.

23 MS. AXELRAD: I think we need an hour, so I would
24 say 1:15, be back here at 1:15.

25 [Luncheon recess taken at 12:10 p.m.]

1 AFTERNOON SESSION

2 [1:15 p.m.]

3 MS. AXELRAD: I guess I am going to leave this
4 open to you all to set the agenda as to where we want to go
5 next. We don't obviously have any planned presentations.
6 What is it that we want to discuss?

7 DR. COLEMAN: I think I would like to know where
8 you are going with FDG and oncology. Jenny just gave you 30
9 or 40, 50 very good articles, some review articles on
10 specific indications, as well as general applications in
11 oncology.

12 A couple of the issues that again relate to things
13 we discussed this morning relate to how the package insert
14 is going to be worded and the general indications versus
15 specific indications.

16 The cardiac was rather straightforward. The
17 myocardial perfusion was rather straightforward, but as we
18 get into FDG and oncology, it is more problematic because of
19 the multiple indications that it has been used in, is being
20 used in, and the ability to supply a lot of data in some
21 cancers which are quite prevalent, the lung cancer,
22 colorectal cancer, some of these, whereas, some of the
23 indications, which are going to be quite effective, are
24 going to be orphan diseases.

25 You know, they are going to be the sarcomas where,

1, you know, a major medical center like Duke might see 10
2 patients a year, very difficult to get large numbers of
3 studies to document its utility, but yet it is going to be
4 there.

5 So, my question to you is how do you see this
6 review of FDG and oncology going, and then how do we factor
7 in these common indications where we are going to have a lot
8 of data, as well as the other indications where there are
9 just not going to be so much data?

10 DR. RACZKOWSKI: That is an excellent question.
11 We are still in the preliminary stages of this review, so it
12 is hard to say how things will play out. I anticipate that
13 much of the review would, in terms of some of the issues
14 with the literature would be similar to some of the things
15 we talked about this morning.

16 One of the things that may help us focus our
17 review, though, I think would be if we had a clear sense
18 from the community what you would like to see in terms of
19 indications or what you are striving for, because it is
20 pretty hard to go into these things open-ended, and it is
21 much more straightforward if we can into it with specific
22 questions that we are trying to answer.

23 DR. COLEMAN: I think that again, like we were
24 talking about with the ammonia, it would be our thought at
25 this point in time that FDG is indicated for evaluation of

1 tumors including lung cancer, colorectal cancer, head and
2 neck cancer, melanoma, lymphoma, and having some general
3 statement followed by a specific indication.

4 DR. CONTI: I think also in line with the nature,
5 for example, of the cardiac literature, where there are many
6 subpopulations, there are many ways of doing the studies,
7 whether you have FDG with rubidium or FDG with ammonia.
8 There is a significant amount of variability within the
9 actual trial designs.

10 One could look at the oncology literature in the
11 same fashion as a whole and say, okay, well, there have been
12 scores of different subpopulations that have been evaluated
13 with FDG for tumor imaging, and pooling all of the
14 literature, not separating it necessarily into lung,
15 colorectal, head and neck, et cetera, and critiquing each of
16 those individual categories, but saying look at the entire
17 spectrum of what we have done with this tracer, like the
18 higher spectrum that we have done with viability, like the
19 higher spectrum that we have done with perfusion.

20 DR. RACZKOWSKI: I think the idea of pooling the
21 data is an interesting one, but that can be done in
22 situations where there is biological or can potentially be
23 done in situations where there is biological or other
24 reasons to believe that the drug is behaving the same way in
25 a different state, in other words, it is harder to pool

1 things that are very heterogeneous if there is not some
2 common denominator.

3 DR. CONTI: Well, there is in, in fact. If you
4 assume that you understand the pharmacology of FDG, which is
5 what I read in your cardiac, and you do know that, in fact,
6 there is accelerated glycolysis, and that is, in part, part
7 of the pharmacology or pharmacological basis of this drug.

8 Well, tumors have that, and that is a well
9 documented parameter in malignancy, there is accelerated
10 glycolysis, so you have the option of extending that concept
11 to neoplasia, and this is really what we are talking about.

12 DR. RACZKOWSKI: I think we would feel more
13 comfortable with the notion of accelerated glycolysis, but
14 in terms of being able to differentiate the different types
15 of tumors --

16 DR. CONTI: We never claimed to do that. An FDG
17 scan is an FDG scan. We don't claim anywhere in any of our
18 literature --

19 DR. RACZKOWSKI: So, that is not something that
20 you would want to --

21 DR. CONTI: I think you are dealing with an issue
22 of accelerated glycolysis as the principle for accumulation
23 of the radiotracer in the tumor, and we can argue about the
24 fine points of what all means in biochemical terms, which I
25 would not opt to do, but the point is that the principle of

1 accelerated glycolysis has been the foundation for the
2 development of this tracer for oncology purposes, and we are
3 not in the position, nor is the literature in the position,
4 to speculate as to whether lung cancer is going to be
5 distinguished from colorectal cancer, et cetera.

6 DR. HOUN: I know we were just throwing out that
7 label suggestion Dr. Coleman was just suggesting. We were
8 concerned that if we would say including head, neck, lung,
9 lymphoma, sarcoma, that that implies differentiation, and
10 that is not something you really were talking about.

11 DR. COLEMAN: That is not our objective.

12 DR. CONTI: As examples, again the "such as"
13 concept, but trying to package it so it is acceptable to
14 your language.

15 DR. HOUN: So, if there were general terminology
16 about used as part of assessment for presence of tumor,
17 presence of neoplasm, those are things that you are looking
18 for.

19 DR. CONTI: Yes.

20 DR. LOVE: Are you looking to differentiate
21 malignant and nonmalignant lesions?

22 DR. CONTI: Yes.

23 DR. LOVE: Would this be something that you would
24 think would replace a biopsy? Do you see that as a label
25 indication perhaps?

1 DR. CONTI: It would depend on the circumstances I
2 would think.

3 MS. TESAR: Not in all cases.

4 DR. CONTI: We have developed, for example, in the
5 lung cancer literature, that is developed to the point where
6 the solitary pulmonary nodule, differential malignancy
7 versus being benign, can be applied to what you are bringing
8 up, which is the avoidance of biopsy. Will you do that in
9 all cases? It will depend on the clinical situation and the
10 type of cancer you are dealing with, so I can't give you a
11 generic answer to that.

12 MS. TESAR: We can use lung cancer as an example
13 and what we have done with Medicare, and you may replace a
14 biopsy depending on the result of the PET scan, but then if
15 you have a positive result, for example, in metastases, you
16 need to determine if that is cancer or not somehow, so you
17 may biopsy the most, you know, outside lesions, so you are
18 not going to be doing maybe a lung biopsy, but you are going
19 to be biopsying a lesion that is closest to get to, just to
20 get that diagnosis, so in some cases, yes, you are avoiding
21 it, but in not all, so it is going to be tumor dependent in
22 that respect.

23 DR. CONTI: Also, that is driven in part by the
24 therapeutic options. For example, we would not like to
25 treat a patient without tissue regardless of the particular

1 modality used to make the diagnosis or the clinical
2 examination. In other words, to apply radiation therapy or
3 chemotherapy, you will not make that decision on the basis
4 of clinical examination or imaging alone. You will need
5 tissue.

6 So, again, it would depend on the particular
7 clinical circumstances. If it is a recurrent cancer, well,
8 you may not necessarily do a biopsy anyway, but you would
9 rely more heavily in that case on the imaging data or the
10 clinical examination to treat.

11 DR. RACZKOWSKI: How about differentiating a
12 neoplasm, either cancerous or benign, from other types of
13 masses, inflammatory or infection, is that something else
14 that --

15 DR. CONTI: It can be considered. I mean there
16 are circumstances where there are certain inflammatory
17 processes which will exhibit elevated glycolysis, just like
18 there is issues of use in the brain where the brain utilized
19 glucose, or issues in the heart where the heart utilizes
20 glucose. There are other entities or disease processes that
21 can have accelerated glycolysis.

22 DR. RACZKOWSKI: So, you are looking to make that
23 distinction now?

24 DR. CONTI: It would depend on the clinical
25 question. I mean I think if you are going to try to

1, distinguish between a person, let's use an example, in the
2 lung, because it seems to be pretty well accepted, and if
3 you have a person with active tuberculosis and a patient
4 with lung cancer, it can be difficult to make that
5 distinction.

6 However, you are using the tracer in that
7 circumstance as a tracer of some level of metabolism or
8 biological activity, displaying an active disease process.
9 Now, the differential diagnosis exists, and you may still
10 act on that information irrespective of whether it turns out
11 to be tuberculosis or cancer, but it allows you to then take
12 the next management step in that patient.

13 DR. COLEMAN: As Peter said earlier, you are going
14 to have to prove that it is cancer. I mean oncologists
15 aren't going to just go on the PET scan, so there will be
16 some false positives with active granulomatous infections in
17 the lung. Those are not very common, but they do exist, but
18 you are going to follow those up to get tissue.

19 So, it is a known area that will accumulate FDG,
20 and it is just one of the -- no test is perfect. Every test
21 has its limitations, and that is one of the limitations with
22 this particular test.

23 DR. RACZKOWSKI: This is such a broad area, it is
24 hard to talk about specifics, but in terms of PET, FDG in
25 relationship to other modalities, such as where it fits in

1, with, say, MRI or CT in terms of the diagnostic sequence of
2 events, or is that something that you would be thinking
3 about?

4 DR. BARRIO: You mean cost effective?

5 DR. RACZKOWSKI: No, no, nothing to do with the
6 cost, but where does it fit. I mean, in other words, you
7 have an equivocal CT scan and you want to follow it up.

8 DR. COLEMAN: Almost all of the data that you have
9 there, the patients will have had a CT and a PET scan, and
10 in almost every circumstance, the PET is going to be more
11 sensitive and specific than the CT scan result.

12 DR. RACZKOWSKI: Perhaps what I am asking is --
13 again, it may depend on the cancer or situation -- are you
14 looking to, let's say, replace some of these other
15 modalities or as an adjunct to -- and if it is an adjunct
16 before or after?

17 DR. COLEMAN: In some circumstances, it is going
18 to replace, but more often it is going to be an adjunct,
19 because CT scanning is just so ingrained in oncology these
20 days, but there are some circumstances certainly where it
21 can replace getting a CT scan done.

22 I can tell you at our institution, our melanoma
23 surgeon no longer gets CTs, he is following with PET
24 scanning. In our lungs, if we see a lung nodule, we don't
25 get a CT, we get the PET scan. So, in some circumstances,

1, it has replaced getting the CT scan.

2 MS. TESAR: In certain recurrent disease like
3 colorectal cancer, there is sometimes a rising CEA, and
4 prior to surgery, there may be a PET scan done prior, and
5 replacing at CT, too, with the rising CEA, so there are
6 circumstances that they do replace.

7 I don't know if we can make a claim that it
8 replaces CT, you know, it can replace CT.

9 DR. CONTI: We don't want to get into that. I
10 think we have to allow the physician some discretion and the
11 local custom as to how patients are worked up to make those
12 judgment calls. What we want to do here is allow them to
13 have the option to use this technology in its best form, in
14 other words, it can image tumors, let them decide what the
15 best place is. The insurance companies will look at this,
16 they will also have some influence on how the management of
17 patients go, but I don't think we want to get into
18 micromanaging medical practice.

19 MS. AXELRAD: We certainly don't. I mean all we
20 are talking about is what kind of claims do you want to
21 make.

22 DR. HOUN: There are some diagnostics which are
23 supposed to be used as an adjunct like to mammography, the
24 ultrasound, the high definition ultrasound was approved as
25 an adjunct to an abnormal mammographic or indeterminate

1, mammographic image, and would you suspect that this
2 literature is more supportive in that direction, where used
3 as a follow-up to CT scan or for abnormal or questionable or
4 indeterminate?

5 DR. COLEMAN: Most of the literature will be a
6 comparison of CT and PET, and will be characterizing CT
7 detected abnormalities. That will be most of the
8 literature.

9 DR. CONTI: That is an important point here,
10 though, is that that is the rationale for the study. You
11 have to understand that. I mean they are doing to study to
12 try to better characterize a particular finding, and it may
13 be CT, it may be MR, it may be other nuclear medicine
14 imaging techniques, whatever the point is, it is an
15 additional test that is being evaluated against some series
16 of standards, whether they are CTs or other, or blood
17 markers or whatever.

18 In clinical practice, however, you might have a
19 situation where the CT is done after the PET scan, and there
20 may be a real dearth of information in that scenario in the
21 literature since that was not the objective.

22 DR. COLEMAN: That is exactly what is happening at
23 Duke in melanoma now. We get the PET scan, and if we see an
24 abnormality, then they will get a CT to use to guide the
25 biopsy, to document that it is metastatic disease.

1 The PET scan is more sensitive and can survey the
2 whole body better than the CT scan can, so I think that we
3 don't want to limit it.

4 MS. TESAR: I think that is an adoption of
5 practice parameters, too, and physician practice patterns,
6 and I think what we are seeing is that initially, it was an
7 adjunct that even came after a CT most of the time, and that
8 is that what our literature represents right now, because
9 that was the standard and we needed to compare it to
10 something.

11 But as you get out into clinical practice in the
12 center that I am involved with, you see the physicians being
13 able to evolve their practice patterns, and they start
14 replacing like they are doing at Duke, where they don't do a
15 CT scan for melanoma.

16 In our institution, you know, rising CEAs, they do
17 a PET study, and certain other tumors, they do a PET study
18 prior to surgery before they would think about doing a CT if
19 there is other suspicion of tumor.

20 So, I think that is a practice pattern thing that
21 we really can't write into a label.

22 DR. CONTI: We want to focus on that being rather
23 than practice, we want to focus on the standards at which
24 PET was compared to, just like in the other studies that we
25 have gone through, what other tests were being used, the

1 echoes and the angiographies and things like this. It is
2 not a question of which is done first, it's a question of
3 what is used as the standard for the particular study, and
4 let the other sort itself out in clinical practice.

5 Once we can get over that concept, then, we can
6 begin to look at the broad issues that this tracer brings to
7 the table with regard to imaging of cancer.

8 MS. TESAR: So, looking at that, what would we
9 need to do? In your estimation, would we need to look at
10 each individual tumor, do we need to look at a broad
11 statement that can encompass the tumors and then have some,
12 where you mentioned before you can have a functional and --
13 what is that next level up -- disease specific, you might
14 cross that line.

15 I don't know what other literature we can do or
16 what we could do to support that, but that seems to be my
17 sense that we would have a functional, then the disease
18 specific sort of level.

19 DR. HOUN: So, in terms of the functional claim, I
20 mean the function is to detect active disease process with
21 increased glycolysis. I mean that is the biochemical
22 process, but in terms of relating that to a claim, a
23 clinical claim, it would be in order to help assess the
24 possibility of malignancy or neoplasm or inflammatory
25 conditions?

1 MS. TESAR: Can you say assess or can you say
2 image, can you say tumor imaging?

3 DR. CONTI: We can give you some examples. We can
4 use terms like diagnose, stage, evaluate for recurrent
5 disease, assess response to therapy. These are generic
6 cancer-related indications, that if you aren't using FDG,
7 you could use a gallium scan, or if you aren't using a
8 gallium scan, you could use a CT scan. You are just looking
9 at what is used now from an imaging point of view how you
10 work up a cancer patient, and can we adopt those types of
11 questions to the FDG molecule.

12 DR. LOVE: I think those terms you were just
13 mentioning are things we can certainly think about. For
14 example, the beginning statement was tumor evaluation, so
15 evaluation for what. We do need some type of context in
16 general, although there are times that we don't, but often
17 we do have some type of context.

18 The issue of replacing biopsy is something that we
19 will have to think about and look at the data. I think
20 something underlying one of the comments Victor was making
21 earlier is perhaps you can't distinguish one tumor type from
22 another, but are you more apt to have a correct answer in
23 one tumor type or another is something that may be of
24 concern or question, and going through the data would try to
25 help answer some of those questions or at least determine

1, what information may need to go into labeling to identify or
2 guard against certain types of assumptions to make sure that
3 there is enough information that is available to the user.

4 DR. COLEMAN: An example of that -- and really
5 didn't include this in the literature -- in lung cancer, PET
6 is very good, very sensitive, but there are some unusual
7 types of lung cancer, not even necessary to call cancer,
8 such as carcinoid tumor of the lung and bronchoalveolar cell
9 cancers, that PET detects probably 50 percent of those.

10 I think that is getting at what you were talking
11 about, there may be certain cell types or certain types that
12 it is less accurate in, and they are starting to be, I don't
13 know, we did a study of 10 or 12 patients, and there is two
14 or three studies now of that many to show the decreased
15 sensitivity in carcinoid tumors and bronchoalveolar cell
16 tumors compared to the other, other non-small cell tumors.

17 MR. CONTI: That may depend, in large measure, on
18 the presentation of the disease and how it appears, if it is
19 a diffuse, disseminated disease as opposed to a focal
20 lesion. There are differences in our ability to detect such
21 lesions just as a technological issue.

22 Don't forget, also, that there is some information
23 in there in looking at the degree of uptake of the tracer
24 with regard to prognosis. For example, brain tumors is a
25 good example of that. There is pretty good evidence about

1 using FDG in brain tumors to determine prognosis in
2 patients. There are articles that specifically address
3 that.

4 DR. COLEMAN: We just had an article in Cancer
5 last month on FDG uptake in lung cancer and its prognostic
6 ability, similar to that in brain tumors. And there is
7 starting to be more of that.

8 DR. RACZKOWSKI: Someone asked me earlier what a
9 good example might be of one of the other claims.
10 Prognostic indicators is probably a very good one.

11 DR. COLEMAN: I thought that was probably it.
12 But, yes; there is starting to be more data on the
13 prognostic information. At the time, the amount of glucose
14 uptake in lung cancer predicts prognosis even if you know
15 the stage of the tumor, the size of tumor, everything else,
16 the FDG provides additional information, so that type of
17 thing is becoming more available.

18 MS. TESAR: One thing, too, that we need to keep
19 in mind is that we are looking at the claims for a generic
20 drug where one company is not going to differentiate
21 themselves from another saying that we do this with this
22 product--we do this better than Company Y.

23 So I think the level that we need to worry about
24 is are we going to get paid for these studies by third-party
25 payors in government and when a company might advertise

1, that, an individual company might advertise that.

2 I don't see how we are going to go head-to-head
3 with this generic FDG.

4 MS. AXELRAD: In a way, you are going head-to-head
5 with the existing diagnostic agent. You are not going head-
6 to-head against each other, or could be, depending on your
7 claim, going head-to-head against thallium or some of the
8 other traditionally approved--and even the devices, the CT
9 scans and the MRIs and things like that.

10 MS. KEPPLER: So it is more important.

11 MS. AXELRAD: Certainly, from the agency's
12 perspective in terms of establishing this and for what kinds
13 of claims you are going to be allowed to make in the
14 advertising, for example, it does have significance.

15 MS. KEPPLER: Okay.

16 MR. CONTI: We want to also level the playing
17 field here. We want to give the physician the choice to
18 decide which tests he or she would like to be able to use.
19 We want to make sure that our claim is not only accurate but
20 it does reflect clinical practice options. So you can
21 choose a PET scan or a CT scan to evaluate that particular
22 patient. That is really what I think we are asking for in
23 this whole process.

24 MS. KEPPLER: This discussion of the prognostic
25 use of lung cancer and brain tumors, and Peter, correct me

1 if you feel differently, I am not so sure we are looking for
2 that to be in the labeling. Are you? Are you guys looking
3 to see that in the labeling, Ed?

4 DR. COLEMAN: I would not, at this point in time.

5 MS. KEPPLER: I just want to make sure. We were
6 talking about it because there is some literature on that
7 and I am not so sure that is a hope, even.

8 MR. CONTI: As I said, there are many different
9 questions that one can ask once you have access to the
10 tracer and some of them, obviously, are going to be less
11 well-supported by what it is in the literature, clearly.
12 But, again, allowing the use in the area of malignancy will
13 open up that channel for access to the drug and I think,
14 then, the literature will follow and we will be able to
15 expand on it as we generate more material.

16 MS. AXELRAD: Let me just sort of summarize where
17 we are in terms of what we need from you. This isn't the
18 end, but where we stand so far sort of on both the ammonia
19 and the oncology. What we need is to really hear from you
20 what claims you want to see on the label for ammonia and for
21 FDG, both myocardial perfusion in that area and, also, with
22 regard to the oncology area and, if there is something else.
23 We haven't really gotten into anything else. We only have
24 literature--

25 DR. RACZKOWSKI: There are other things like

1 Alzheimer's disease.

2 MS. AXELRAD: We have some literature on that.

3 DR. RACZKOWSKI: That is an area that you are
4 interested in.

5 MR. CONTI: Yes.

6 DR. RACZKOWSKI: What we were thinking of doing--
7 we were debating at lunch the merits of doing this--but
8 giving you the label for FDG, for example, and circling the
9 sections that we think it would be useful to get input from
10 you on; what is the dose, what does patient preparation look
11 like, what are the claims that you want, so we could
12 actually get something specific from you.

13 It is one of the other review divisions at the
14 agency has talked about is developing a label in advance so
15 the development program and then tailoring your development
16 program to get to where you want so you don't do your
17 development program and then find it is over here and the
18 labeling you want is over there.

19 So, in a way, it could be helpful for us to get
20 that kind of information from you. I would like to see what
21 are your views about that. That would be one of the things
22 that we were talking about proposing.

23 DR. COLEMAN: I think we had talked about that
24 today with cardiology. It was our understanding that we
25 were going to be getting our thoughts together and getting

1 them to you about what we would like to see the indications
2 include. Again, at lunch, we were talking about, hopefully,
3 the same thing could go on with oncology. We would be happy
4 to respond to questions concerning those patient
5 preparations.

6 In some of those, the patient preparation is very
7 easy in most other than cardiology and the FDG uptake
8 because of the insulin and glucose influence. But, no; we
9 would love to work with you on that. Certainly, we could
10 come in with our recommendations or we could take whatever
11 you have and discuss it and fill in the blanks.

12 MS. AXELRAD: I think we would really like to get
13 your recommendations. First of all, we have sort of heard
14 where we are already on ammonia and FDG for myocardial
15 perfusion. So it would be useful to know how far off what
16 you want that is. I think the earlier we hear what you
17 really think, what you really want, for oncology, before we
18 get into the review, because then we can sort of look in
19 those directions and ignore some of the other things that
20 might catch our attention and we won't waste a lot of time
21 looking at prognosis if you are not really interested in
22 that.

23 We can focus our review on the claims that you
24 really are interested in. And then I want to talk a little
25 bit about--one of the things that we have heard a lot about

1 is the utility of multicenter trials. Again, we are going
2 to be doing the work and we want to talk to you also about
3 what other compounds we might want to do this kind of a
4 literature review with.

5 We are only talking maybe one or two at most. You
6 can see what kind of work has gone into doing this. We just
7 really don't have the resources to do this. So we have to
8 get to the point where what we do leaves off and what the
9 PET community can do in terms of pulling the data together
10 and essentially proving these claims.

11 What are you able to do? I mean, are you able to
12 do a prospective, multicenter trial? Is there some focal
13 point? Can ICP, with somebody who has control of how the
14 drug is manufactured, do something like pulling together an
15 IND and doing a protocol that would be done at multiple
16 centers that would generate prospective data for new
17 indications, for example.

18 If the prognosis thing develops into the point
19 where you think it would make it, how would that get pulled
20 together and presented to the agency and what will happen
21 with regard to anything that we don't do this way. What can
22 you do? What is realistic for us to think about the
23 community doing?

24 DR. COLEMAN: I think that is a very interesting
25 and difficult question. Let me just tell you, ICP has

1 organized two clinical trials so far, one of which was
2 published--I don't remember, Jenny, did we have that in
3 there?

4 MS. KEPPLER: Yes; it is in there.

5 MS. TESAR: Single pulmonary nodules.

6 DR. COLEMAN: Pulmonary nodules. That was done by
7 us at Duke doing all the coordination. All the studies were
8 sent in to Duke. We made sure they got sent out, read
9 blindly, et cetera. That would be very difficult to do
10 again.

11 DR. RACZKOWSKI: When you say "we," are you
12 referring to Duke University?

13 DR. COLEMAN: Duke and the participating
14 institutions. They had to send the CT scans, the PET scans,
15 to us, clinical report forms. We had all of this for all of
16 these patients that were filled out at the local
17 institution, send to Duke, collated. Then the films were
18 sent out for blinded readings. The readings came back and
19 all that was done at Duke, coordinated through ICP.

20 MS. TESAR: It is all done as a volunteer effort,
21 though. Duke used its resources. That is how we have done
22 this for everything because we aren't a drug company. There
23 are PET manufacturers but they are not an Eli Lilly, by any
24 means. The resources are limited so most of these--
25 everything has been done with that volunteer effort.

1 We get a little bit of help from companies by
2 using their staff and using their resources sometimes, but
3 it really has been a massive amount of volunteerism. Duke
4 and several other institutions really pull together and use
5 their time and resources to do that.

6 I don't know what we can do in the future in terms
7 of funding. We realize this is a necessity. We tried to
8 put this in the agenda for the ICP and for the PET community
9 every year and try to fund more trials and be able to at
10 least help some of these volunteers in pulling this
11 together.

12 But it is, of course, as you know, time-intensive
13 and money-intensive.

14 MS. KEPPLER: I think one of the other issues,
15 too, is--and if we could solve the coordination problem, I
16 think the issue that we discovered with the adjunct to the
17 NDA for lung cancer is putting the data together in a format
18 that you all are used to seeing it cost us--and Ed you will
19 have to say--\$200,000 and some which, for a series of
20 volunteers trying to put in their \$50 is a lot of money.

21 DR. COLEMAN: And it was found to be unacceptable
22 by the FDA, too.

23 MS. KEPPLER: That is the other piece of the
24 clinical trials. We have got the clinical trials that were
25 done and were published, but that is a different level of

1 data than what you are used to seeing. Obviously, we can
2 control the publication and make sure it had all the right
3 things in it as we are learning that, going forward, but I
4 know putting together the quintiles analysis for the lung
5 cancer was \$200,000 and some which was taking the case
6 report forms and analyzing it.

7 DR. HOUN: Have you talked to folks at the NCI
8 Diagnostic Imaging Branch?

9 MR. CONTI: Their first meeting is at the RSNA,
10 actually, the Akron are you talking about, the NCI-funded--

11 DR. HOUN: Yes; and they also started, I think, in
12 this coming up December--they are starting what is called a
13 network. I think Dr. Dan Sullivan and Barbara Croft are
14 going to be talking about a new network, an oncology
15 network, among institutions to try to help do clinical
16 trials.

17 It is for oncology indications, specifically for
18 imaging. So they might be able to help.

19 MR. CONTI: Right. That is certainly one
20 mechanism that we need to look at. The problem that I see
21 in that is that it is competitive. It is going to be a
22 competitive process for access to funding. We can't do the
23 type of thing that we are doing in the hopes that we are
24 going to be successful in getting funding by applying for a
25 grant, so to speak, to do the trial.

1 If we are going to decide to do a trial, we need
2 to be able to do it and not go through a peer-review process
3 to decide whether the hypothesis is fundamentally sound and
4 things like this. This is something we are going to have to
5 determine as an industry and just go ahead and do it.

6 One of the advantages, for example, of some of the
7 oncology groups and radiation-therapy groups is that they
8 have access to core funding that is available if the
9 committee in the GI section or the colorectal section
10 decides, "Well, we want to do a trial with this new drug,"
11 and they just access a core statistical base, the
12 availability of drug and things like that, so all the core
13 resources are there.

14 Then it is a matter of the investigators to accrue
15 patients and conduct the study.

16 DR. RACZKOWSKI: I don't know what the NCI
17 Diagnostic Imaging Network is going to be but a number of
18 the NIH networks are just that, pediatrics, for example, or
19 neonatal networks. They basically fund the infrastructure
20 for doing the clinical trials.

21 MR. CONTI: In the radiology group, what we will
22 go up against is everyone wants to do a trial, an MRI.
23 everyone wants to do a ultrasound. Everyone wants to do it
24 with conventional nuclear medicine and PET, et cetera, et
25 cetera, that all these groups vying for a single pot of

1 money that we are going to have to submit an application
2 for. If we get turned down, it may be another full year or
3 two years, three years, before we get access to actual
4 funding to do a study.

5 DR. COLEMAN: We certainly know Barbara Croft and
6 Dan Sullivan well. We know that mechanism. At this point
7 in time, there is no specific PET protocols in that. Barry
8 Siegal is on the main committee. I am on Barry Siegal's
9 Committee on Nuclear Medicine and PET that will be looking
10 at protocols to be supported there.

11 The other multicenter study that is being looked
12 at is through the American College of Surgeons. They are
13 planning on doing a lung-cancer and esophageal-cancer
14 multicenter study. I don't know where or how. It is one of
15 those things, like Peter was saying, if you don't have a
16 company interested in doing it, moving ahead, you have no
17 control of when it gets done and there is a lot of delay
18 that comes through that.

19 So we would love to do more multicenter studies
20 and that is something that we would like to do at ICP. But
21 the funding mechanisms are the problem.

22 MS. AXELRAD: This is really the crux of the
23 problem. We can take this so far by doing whatever we are
24 doing with the literature review and coming out with some
25 conclusions. But you are still left with every new

1, indication doesn't make it now and every new molecular
2 entity. The question is what procedures and what shall we
3 do.

4 I think that--well, I don't know. I'm not sure
5 you have ever suggested what it is you foresee out of this.

6 DR. BARRIO: That is why we were thinking that
7 these five--the way we see this problem is if we are talking
8 about a new PET radiopharmaceutical that doesn't exist right
9 now, and then, let's say, USC developed that one, then they
10 may have the incentive to produce a patent for that
11 particular radiopharmaceutical and to go through the process
12 of the clinical trials by themselves, either they have the
13 money or license this to industry.

14 And then industry would have a reason for doing
15 this, spending whatever number of dollars. Then they have
16 the NDA and then it is like we do any convention drug
17 approval or radiopharmaceutical approval.

18 The question we have is, beyond these five
19 radiopharmaceuticals we are trying to consider now is where
20 they are in between. There are more than 3,000 or 4,000
21 radiopharmaceuticals synthesized and using research, many of
22 them frequently, most of them very infrequently. Then some
23 of them may emerge as potentially useful compounds.

24 I can think about one, carbon 11 acetate, that,
25 for example, at Washington U, is being used clinically.

1 Now, the question is what do you do with something like
2 this? There is no particular incentive for anybody to
3 really go beyond because it is a lot of money.

4 MS. TESAR: We can't distribute it. It has got
5 too short a half life to distribute, really.

6 MR. CONTI: A generic drug is whatever would be
7 patented and developed through industry. And the spectrum
8 of generic drugs is rather large.

9 DR. COLEMAN: Absolutely.

10 MR. CONTI: And will never really have an owner.
11 And we may be stuck in that quagmire of having to only rely
12 on the literature as it is developed. It may take years to
13 develop the literature on certain kinds of drugs as they
14 emerge versus actually coming up with the funding to do our
15 own public, if you will, approach in evaluating this in a
16 clinical trial.

17 MS. AXELRAD: There are options. First of all,
18 the drug can be made available under INDs in a research
19 setting, if it is just purely research and not clinical at
20 all, under the existing RDRG thing. It can be made
21 available under and IND in the clinical setting also.

22 DR. BARRIO: Is it possible to do that, to make it
23 available in the clinical setting under an IND?

24 MS. AXELRAD: Yes.

25 DR. BARRIO: And get reimbursed, too?

1 MS. AXELRAD: No; not and get reimbursed. I
2 wasn't going that far. I was just sort of taking it
3 stepwise. We are getting to that.

4 DR. BARRIO: That's what I was wondering.

5 MS. AXELRAD: But when you want to take it from
6 the investigational stage to the clinical setting and you
7 want to get reimbursed, then somebody has to do the work
8 that we did or are doing for these. That is what we have to
9 talk about. I really think that the literature review that
10 we did for this is the bare minimum of what can be done.

11 There are not only the new things that may sort of
12 emerge from research but there are the ones--you talk about
13 five. We really only committed to doing four. When you get
14 off to the f-dopa where it is a receptor agent, my
15 understanding is that that gets a little trickier.

16 DR. BARRIO: No; it is not the receptor agent. It
17 is a neural transmitter. It is non-toxic.

18 MS. AXELRAD: Okay; sorry. But it gets more
19 complicated to do a literature-based review of that. We
20 haven't really talked about that at all but we can, at some
21 point, at one of our future meetings talk about the
22 difficulties associated with that.

23 So the question is, first of all, is the
24 literature on that developed to the extent that the
25 literature here is so that you can pull something from it?

1 What are the difficulties associated with pulling anything
2 together from the literature on that and who would do it?

3 Would we do it or is there somebody in the PET
4 community, either ICP or whoever, who can do that?

5 MS. TESAR: To search the literature and do an
6 evaluation.

7 MS. AXELRAD: To do what we did. To do the
8 analysis. It's the analysis.

9 DR. BARRIO: We can do that. In fact, we have
10 done it with fluoro-dopa already partially. That is a field
11 I have been working in for years, the animal models and
12 everything else. I know that literature very well. Then I
13 will be more than happy to help you go through that process.
14 And I understand. You have shown us this morning and this
15 afternoon all the work you put together to do it.

16 This is extremely time-consuming. This is a very,
17 very difficult process. We appreciate that.

18 On the other hand, for us it is so important
19 because otherwise we are left with this vacuum that is very
20 hard to fill. One of the things I would like to see, too,
21 Jane, is, once we decide on four or five, how to deal with
22 the potential emergency of one or two from this jungle of
23 radiopharmaceuticals that may end up being in the clinical
24 trial, what kind of requirements you might like to put
25 together considering that there is no incentive in industry,

1 no incentive in the PET community, beyond those who really
2 want to do it, to really go through the clinical-trial
3 process and do it that way, what kind of thing we could do
4 under this circumstances.

5 MS. AXELRAD: The incentive, though, is to get
6 reimbursement for it and then make money off of it. That is
7 the incentive. At some point, that becomes a large enough
8 incentive to do something. The question that is given to us
9 from the Congress, really, in terms of implementing the
10 statute, is what is required, what do you have to show, what
11 kinds of procedures and requirements.

12 We can try and articulate in a guidance document
13 or whatever vehicle we choose to use, what our expectations
14 are. We are taking steps in the radiopharmaceutical
15 diagnostic area, in the traditional radiopharmaceutical
16 diagnostic area. There are some of the same issues.

17 Can you distinguish between class 1 and class 2
18 products, the ones that have a sort of clear safety profile
19 from the ones that are a little more difficult, can you
20 simplify the requirements for one category as opposed to a
21 second category, can you differentiate what is required in a
22 trial based on the claim that you are going for.

23 And then the question is what other kinds of
24 things can we clarify or explain? Certainly, orphan drugs
25 are developed all the time where there are very small

1 patient populations. We are not inventing something new
2 here. Small companies develop orphan drugs presumably with
3 a relatively reasonable amount of money or else they
4 wouldn't be doing it.

5 There are ways of sort of taking those concepts
6 and trying to articulate them in the PET area in a way that
7 I hope will be applicable. But if the answer is nobody is
8 going to do anything and you won't do any kind of clinical
9 trials because there is no way of doing that then there is
10 not a lot of point in spending a lot of time trying to
11 articulate how you do that.

12 MR. CONTI: I think we have to make sure we
13 understand it. I think there has been a lot of confusion
14 over the last several years as to what the requirements are.
15 We are in the process now of defining those parameters.
16 This is very important, I think, for the community to go
17 back and reassess whether it now is doable.

18 In other words, if we are going to do a literature
19 review what it is we are, in fact, expected to do, if we are
20 going to do a clinical trial what it is we are expected to
21 do, how many patients, what type of study, what are the
22 parameters of those studies.

23 This has escaped the PET community over the last
24 decade and, therefore, there has been very little on our
25 part to try to figure out, "Well, gee; we don't know what we

1 are going to do." We run into the problem that we ran into
2 submitting the lung-cancer data we submitted. We spent
3 \$200,000 on it. It goes to FDA and they say, "Well, this is
4 not in the format that we want."

5 That can't happen.

6 MS. AXELRAD: I want the record to be clear. That
7 is not my understanding of what happened.

8 DR. LOVE: No. And I think Kim called you to try
9 to talk about that. There clearly was some miscommunication
10 there. The main issue--and here is Kim. Maybe she would
11 like to articulate some of this. Kim, we are talking about
12 the issue of the single pulmonary-nodule study and the
13 communication that you and Jennifer had and whether we truly
14 were saying it was not acceptable.

15 We were not saying that it was not acceptable.
16 What we were saying, though, was that the information we
17 needed to review, we were going to review it in the manner
18 somewhat of a pre-NDA and we needed more communication with
19 you. But we had not said that it was not acceptable.

20 MS. KEPPLER: I think the crux of the problem is,
21 and this isn't going to go away with any other generics
22 which raise up, which is the ICP or professional association
23 can't get an IND. It has to be done by some institution
24 somewhere. The same thing with an NDA.

25 So, as we go forward with the generics, if we are

1 the process yet. We haven't even attempted to clarify the
2 process yet.

3 MR. CONTI: This is my point. I think the issue
4 is as we define what that process is, it will be much easier
5 for the PET community to decide what it is we can and cannot
6 do. If the parameters are well defined, I think, and I
7 guess I sort of speak in part for a good portion of the PET
8 community, that there will be a response from the Society of
9 Nuclear Medicine, from ICP and other organizations and
10 industry that we will be able to pull together the types of
11 trials that you would like.

12 If the parameters are designed such as they are
13 acceptable by both groups, we will do what we can and this
14 is a commitment that I think we have to make to FDA to do
15 these trials.

16 DR. LOVE: And I think that it is important what
17 you are saying about our ability to communicate because I
18 think that example that was just put on the table was a
19 problem of communication and it was for that reason that we
20 contacted Jennifer because when we recognized the
21 miscommunication, we called to try to straighten it out.

22 But I think the process, clearing up exactly what
23 the issues are and what are the things that both of us need
24 and where are we going forward is the important thing. So,
25 clearly, there was miscommunication.

1 MR. CONTI: Do you believe that there is a
2 mechanism for a DMF or let's say an NDA, if you will--let's
3 use that term just for sake of discussion--that can be
4 publicly held or that can be done through a professional
5 society?

6 MS. AXELRAD: Yes. I think an IND might be able
7 to be done through ICP. I want to look into that legal
8 question. I am certainly not going to say right now you
9 can't do that. I think that is an important legal question
10 we have to answer.

11 MR. CONTI: I want to get beyond the IND, though.

12 MS. AXELRAD: I know, but the IND--clearly,
13 anybody can hold an NDA. Yes; there could be a publicly-
14 held one and you can charge people for granting them access
15 to your data. We can figure out whatever we want in terms
16 of procedures. DMF is what the traditional way of--where
17 proprietarily-held data is, where you are not giving
18 everybody the data, you are giving them access to it and you
19 share it, or somebody shares it with us.

20 And we keep it confidential and they give a right
21 to reference it to other people. That is sort of the way it
22 is done, not usually for clinical data, mostly in the
23 chemistry context.

24 We have flexibility. We have to watch the statute
25 and we can't do anything that is inconsistent with the

1 statute and there are certain things we would have to look
2 at, but we could do new regs. We are obviously supposed to
3 do new procedures. If we need to do it by regulation that
4 sets out special procedures, we can do that.

5 MR. CONTI: I think that is the issue for us. We
6 have a generic-drug issue that not going to go away.

7 MS. AXELRAD: We still call it a generic-drug
8 issue. Bob Wolfangel wants to say something and since he is
9 practically the only member of the audience--

10 MR. WOLFANGEL: Thank you. Listening to the
11 comment that was just made with respect to ICP, I just sort
12 of want to put in a plug for using the USP as, perhaps, a
13 holder of an IND and NDA and work through that process as
14 well. That would be unusual.

15 MS. AXELRAD: That would certainly be unusual.

16 MR. WOLFANGEL: But it may, in fact, be a vehicle
17 that would serve both FDA needs and also the needs of the
18 PET community. So I just offer it as an alternative.

19 DR. LOVE: The other part on that has to do with
20 ICP's legal construct and the risks that ICP is willing to
21 assume because there are two sides on this particular issue.

22 MS. AXELRAD: I think we need to start identifying
23 what the issues are with this part of it. We can start
24 clarifying--in fact, one of the take-away items I have is to
25 go back and start thinking about what kind of guidance we

1, can give you in terms of developing a new indication or
2 developing a new molecular entity yourselves.

3 We are learning from doing this literature
4 reviews. We know that we had to piece things together like
5 a jigsaw puzzle. Supposed we just set out at the beginning
6 to do two adequate and well-controlled clinical trials.
7 What would they look like? Ten patients? Twenty patients?
8 Fifty patients? 500 patients?

9 What are we talking about? How many are we
10 talking about? What kinds of claims would you be getting?
11 What kind of analysis would you be getting--so that we can
12 sort of try and reach some kind of an understanding of what
13 has to be done that we can articulate so that the product
14 that you produce, if you do it the way, is okay.

15 MS. TESAR: What we have done today and being able
16 to learn how you did the literature review, what you found
17 in the literature review, I think we can help do literature
18 reviews. That gets us out of the starting gate. That gets
19 the PET community reimbursed. We are able to start paying
20 our phone bills again.

21 We are out of the starting gate. Then, I think
22 what we can look at is that certain entities will arise that
23 want to have proprietary drugs and that want to do these
24 things and then how do we provide access to those?

25 What process are we going to use for the new drugs

1, as we discussed. But I think to get out of the starting
2 gate and essentially what you have done, I think the ICP can
3 certainly help with this review. If we do it with the
4 guidelines that we all agree on, then you will trust that we
5 are going to do it in a good fashion and that you can review
6 what we've done.

7 I think we can certainly help with that. I think
8 my worry is getting beyond that at this point in time where
9 we don't have the means to do that type of search. But our
10 volunteer effort can--we can do literature review. Most of
11 the people have been involved in writing it. Maybe we ought
12 to not have those people do it.

13 MS. AXELRAD: I don't know that they are there to
14 write it anyway. I'm sure the people in the drug company
15 who are involved in doing some of the studies do the write-
16 up. Before you go too far down that road, I would like to
17 sort of see if there is some model. What you saw from us
18 what sort of typical--not exactly typical but a more or less
19 typical FDA review that is done.

20 But what comes in to us--it is similar, but it is
21 an analysis that might be done a little differently than the
22 way our own review is done. So we have to look at sort of
23 how--turning that around to what we would want you to--let's
24 just say you we decided you were going to do the thing on f-
25 dopa. What would we want you to give us so that we could

1, then review it? We would have to sort of look at that and
2 focus on that and articulate that to you.

3 MR. CONTI: I think that is the most important
4 thing. That would help us because, as George said, there
5 are other generic drugs that are out there and there is some
6 literature. But we would like to be able to--I used the
7 wrong word again. I used the "g" word for the record.

8 MS. KEPPLER: Unproprietary?

9 MS. AXELRAD: You don't want to call it a generic
10 drug because the first drug that comes in isn't a generic.
11 It is going to be a new drug application of some sort. The
12 second one that comes in, if we were to go that route and
13 call it a generic, would be a generic.

14 But if it is a generic, then it comes under 505(j)
15 and there are all kinds of issues associated with that. So
16 I want to really stay away from the term generic.

17 MS. KEPPLER: Unproprietary? How about that?

18 MS. AXELRAD: Unpatented?

19 MR. CONTI: There is some literature out there on
20 many of these other agents. If we were able to compile some
21 of that literature in the format that you are looking for or
22 at least evaluate the parameters that you are looking for
23 then we would know where we stood on many of these
24 pharmaceuticals and we would know what other tests would be
25 needed to be done, what other trials would need to be done.

1 DR. BARRIO: Then the first step would be for us
2 to help you in whatever way we can in the evaluation of
3 these radiopharmaceuticals for four--okay, four.

4 MR. CONTI: Let's make a compromise on this.
5 Let's let them prepare the four and you do the fifth,
6 George. How about that?

7 MS. AXELRAD: I think that is a good idea.

8 DR. BARRIO: We could do that. No question about
9 that.

10 MS. AXELRAD: I don't know what the fourth is. I
11 know the third one is water.

12 DR. BARRIO: Sodium fluoride.

13 MS. AXELRAD: Sodium fluoride is the fourth? I
14 just want to make sure we are all in agreement on that is
15 what the fourth is.

16 DR. BARRIO: By the way, most of the literature is
17 really all available, sodium fluoride in 1972, NDA.

18 MS. AXELRAD: And we were modest in the 2,000
19 articles that exist on FDG; right?

20 DR. BARRIO: I think there are much more than
21 that.

22 DR. LOVE: There may be some manufacturing
23 questions or differences that we would try to make sure that
24 the two products are similar. That is what we need to know.
25 You were saying the first thing, though, was really the

1 information on the indications and such.

2 MS. AXELRAD: We want to get this done. We want
3 to get ammonia and FDG done and to the advisory committee,
4 if we are going there, and out so that people can be doing
5 whatever. And then we will do the others. We can start
6 doing the other two as soon as we finish these and have
7 people to do them.

8 We can't lose sight of the chemistry on this
9 because one of the issues--we were spending time discussing
10 that this is safe and effective and kept asking ourselves
11 what exactly is safe and effective because the drug wasn't
12 one drug used in these trials.

13 There were multiple drugs made different ways
14 through different chemical processes. That is not the norm.
15 Normally, we know exactly how the clinical trial material
16 was made and it is usually only made more or less one way.
17 It may change during the clinical development program but
18 then there are measurements of how the new material compares
19 to the old material so you don't have to go repeat all the
20 studies.

21 But we have to sort of keep that in mind. I don't
22 think it is an insurmountable problem with regard to FDG and
23 ammonia but it is something we will be addressing in the
24 chemistry area, what is the chemistry going to look like for
25 these for either an IND or an NDA. What kinds of

1 information do we need and what kind of control or controls
2 over the process do we need.

3 MR. CONTI: I'm glad you mentioned that IND in
4 your sentence there because I think it is really important.
5 To the extent that we can overlap those processes, it would
6 be very helpful and we won't have to go back and do
7 something again that is different just because it is a
8 different structure of an application.

9 MS. AXELRAD: The ideal is you get an IND first
10 and it is like steps. You get the IDE so you can get the
11 NDA and then you go through doing what you have to do and
12 then you get the NDA. You require a certain amount of
13 information to be able to put it into humans in the first
14 place which, presumably, you will have done some of this
15 under your RDRC before you ever get to point of starting to
16 do an IND.

17 MR. CONTI: That is another thing I would hope
18 that you would address, too, in chemistry is the RDRC and
19 what the boundaries are for those radiopharmaceuticals.

20 MS. AXELRAD: We are working on that. We were
21 working a long time ago, way back when we started doing PET
22 and, since we hadn't put anything out, Congress didn't
23 revoke when they did everything else. But we have been
24 working on changes to 361.1 for some time trying to draw the
25 boundary what is under RDRC and what isn't.

1 MR. CONTI: Knowing what you are doing with that
2 would be extremely helpful for us because we are trying to
3 solve a larger problem here which is what pathways do we
4 need to go down with these new compound developments. That
5 communication would be extremely important, I think.

6 MS. AXELRAD: How much can you do under RDRC and
7 at one point, do you need to go to an IND.

8 MR. CONTI: Right.

9 MS. AXELRAD: I think we should talk about that at
10 a future meeting. We can talk about the chemistry, too, at
11 a future meeting.

12 MR. CONTI: With respect to the issue of the
13 potential for public entity or some such equivalent to hold
14 one of these DMFs or NDAs, maybe we should surface the issue
15 of fees and things like this a little bit and see where we
16 are and where you folks are with regard to fees.

17 I think just in the beginning to say that we have
18 already expressed our poverty level with running clinical
19 trials for you, but I do want to approach this a little bit
20 such that we can tie a low barrier to access to some of
21 these non-proprietary pharmaceuticals as opposed to those
22 that are proprietary and what your opinions are on that.

23 MS. AXELRAD: Basically, the statute specifies
24 what we do in terms of user fees. It says that a new drug
25 application, as defined in the statute, pays a fee and the

1 application fee for the fiscal years 1999 and 2000 is
2 \$267,606 plus whatever adjustment we have for inflation.

3 Now, the first new drug application pays that.
4 The first 505(b)(2), which is a special kind of new drug
5 application--for example, one based on the literature--would
6 pay a fee if it is for a new indication, something that
7 hadn't been approved before such as an oncology indication
8 for FDG or a new active ingredient, a new molecular entity
9 if it were based on the literature such as the ammonia.

10 Now, the first one of those would pay a fee.
11 After the first one pays, none of the others would pay a
12 user fee and they wouldn't be generic drugs. They would
13 probably be 505(b)(2) applications all relying on the same
14 safety and efficacy data which would come out of whatever it
15 is we publish. They would not have to pay a fee.

16 Now, if somebody doesn't want to pay a fee at all
17 in the first place, although theoretically the fee could be
18 split between however many people were going to be accessing
19 the data. It could be dealt with through charging for the
20 data if some central group were going to pull it together.

21 If you wanted to not pay a fee at all, the statute
22 provides for certain kinds of waivers and exemptions.
23 Basically, the main provisions are that a waiver or
24 reduction is necessary to protect the public health, the
25 assessment of the fee would present a significant barrier to

1, innovation because of limited resources available to the
2 person, that fees to be paid by such a person will exceed
3 the present and future costs incurred by the secretary.

4 And there is another one that we never use so we
5 don't have to worry about it. Now, what those three sort
6 of--well, the first two, the public health and innovation--
7 depend on is that the entity that is with the application
8 doesn't have a lot of revenue. It is not only the person
9 who submits the labor but also its affiliates.

10 So if you had a small community hospital or
11 something like that that didn't have a lot of annual revenue
12 and wasn't expecting a lot of annual revenue from the drug,
13 they might qualify for a waiver from that.

14 If a not-for-profit group submitted it, they might
15 qualify for a waiver. But, basically, they would apply a
16 financial needs test to determine whether they were
17 qualified. There is also a small-business exception for the
18 first application that is submitted. It used to be a half-
19 fee waiver but now it is the full fee. And that qualifies a
20 small business as someone who has less than 500 employees.
21 We consult with the Small Business Administration who
22 evaluates some of the Small Business Administration rules
23 for determining whether somebody qualifies as a small
24 business.

25 MS. KEPPLER: Gee, the ICP might qualify.

1 MS. AXELRAD: That's an interesting possibility.
2 But, basically, we would have to go through an analysis like
3 that and you would have to keep that in mind when you are
4 setting up whatever process or structure you are going to
5 use for submitting an application to do that.

6 Like I said, I think it would only be an issue for
7 the first application for a new molecular entity or the
8 first application or something or whatever it would be for a
9 new indication. After that, it wouldn't be a problem.

10 DR. COLEMAN: Are these going to pertain to what
11 we are talking about here today with FDG, ammonia, water--

12 MS. AXELRAD: We are.

13 DR. COLEMAN: These will pertain to that, too.

14 MS. AXELRAD: Yes. There is no real basis in the
15 statute. There is no basis at all for us to just say, "Oh,
16 well, we think it would be nice to waive user fees for PET
17 so we are going to do that." We would have to go through an
18 analysis under the provisions and the statute using the
19 parameters that provide for a waiver or exception to do
20 that.

21 MS. TESAR: Who would be waived? Would it be
22 the ICP or the first "who?"

23 MS. KEPPLER: I think she is going to look up to
24 see whether an entity like the ICP could be the holder of a
25 505(b)(2) just like the NDA and the IND.

1 MS. AXELRAD: I don't understand why they
2 couldn't. I don't think there is an issue about that. If
3 ICP wanted to submit the application, they could.

4 MS. KEPPLER: We submitted the DMF, I think.
5 Somebody else correct me, but Peoria holds the NDA. I
6 wasn't around so I don't know why. But I would have
7 presumed that there was a reason.

8 MR. CONTI: There were some reasons. Ed, you were
9 around at the time. I don't remember.

10 DR. COLEMAN: I thought we were told at the time
11 that the NDA had to be at a site and that ICP couldn't hold
12 the NDA. We could hold the DMFs but we couldn't hold the
13 NDA.

14 MR. CONTI: ICP was not actually producing
15 material.

16 MS. AXELRAD: I don't think that matters. Drug
17 companies submit applications and their materials produced
18 at a contract facility. I wasn't here doing this when they
19 did so--

20 DR. COLEMAN: I was. We were told ICP couldn't do
21 it at the time and it had to be the Methodist Medical
22 Center.

23 MS. AXELRAD: I have to find out if there was a
24 legal reason for that or if it was just a preference or
25 what.

1 DR. COLEMAN: I can't remember why, either, but we
2 certainly held the DMFs and we wanted to hold the NDA. But
3 we were told it had to be Peoria. And then they got a
4 waiver on the fee on the NDA.

5 MS. AXELRAD: Right, because they were small,
6 public-held. I remember that. The was one of the first
7 waivers in '93, I think it was.

8 MR. CONTI: Certainly finding that out is going to
9 be important and certainly knowing what are the requirements
10 for actually submitting what you would have to submit to be
11 assessed for an exemption or for a waiver, what ICP would
12 need to put together.

13 MS. AXELRAD: That's easy. I can tell you that.
14 It is handled by the Office of Chief Mediator and Ombudsman.
15 You can call them on the phone and ask them. I can tell you
16 sort of, basically, but they are the ones that actually do
17 it.

18 Basically, it is a letter requesting a waiver,
19 reciting the statutory grounds and indicating what your
20 annual revenue is and things to demonstrate that you had a
21 financial need to get this. You might want to talk to them
22 about how they would react to a trade association doing that
23 on behalf of the industry.

24 MR. CONTI: That is a process that we could start
25 to think about very shortly.

1 DR. BARRIO: I have two questions, Jane. One is,
2 then, you envision for these four or five
3 radiopharmaceuticals that we are talking about right now,
4 five NDAs, to be in place, probably paper NDAs. Those will
5 come from ICP? That is the first question.

6 The second is since we already have an NDA in
7 Peoria for FDG, what is going to happen with that NDA in
8 your view, or how the old NDA will be put together with the
9 present evaluation of the whole process.

10 MS. AXELRAD: I don't think we have talked about
11 that at all and I think we should talk about it. The way I
12 see it is, frankly, that every PET center--don't have a
13 heart attack--every PET center would submit an NDA what
14 would essentially be a paper NDA, a literature-based,
15 505(b)(2) application for the PET drugs and the indications
16 that they want.

17 They will all be the same. They will all sort of
18 follow a model. For the safety and efficacy piece, it will
19 say to reference either the FDA review or the FDA Federal
20 Register Notice or whatever it is that the FDA produces in
21 terms of its analysis of the safety and efficacy of those
22 products or those indications.

23 That would be part 1 of the efficacy and the
24 labeling, whatever it is that we come out with that says
25 this is what the labeling is. The second piece will be the

1, chemistry. What we are working on is some kind of a very
2 standardized chemistry submission that would say, "okay, if
3 you are using this process, do this."

4 Either there is some standard to certify that you
5 are using these same procedures or, if you are not using the
6 same procedures, explain what you are doing differently but
7 it would be a very sort of standardized--as standardized as
8 we can make it given that there are a lot of different
9 procedures out there--piece that describes the chemistry.

10 We haven't talked among ourselves whether there
11 will be other kinds of biopharmaceutics or whatever else
12 there might be. But I really envision a very simple thing
13 that any one of them can do and, really, would be basically
14 differentiating their manufacturing operation from whatever
15 it is that the standard is and saying that they meet the USP
16 specifications, the monograph standards and things like
17 that.

18 That is sort of my vision of this. We don't know
19 if we are going to get there, but--

20 DR. BARRIO: I was thinking probably--I don't know
21 if this is feasible or not, but if ICP had the standard
22 presentation and then the individual centers will send you a
23 page or two indicating, "We use this procedure and we comply
24 with our requirement," that may be the easiest way out
25 rather than every center sending you a pile of papers.

1 MS. AXELRAD: Right. We could probably do that,
2 do it in an NDA, do it in a DMF, whatever, if the bulk of it
3 is there. But they would have to show that they do that.
4 My understanding is that the 70 different PET centers do
5 things somewhat differently. We will have to come to grips
6 with that there are at least two or three different
7 processes for doing this and different levels of procedures.

8 The more that have the standard, the easier it is.
9 If all you are doing is saying, "I am doing exactly the same
10 way as somebody else," and we have already said that the way
11 they are doing it is okay, that is perfectly easy. It will
12 be how to deal with differences, if somebody is actually
13 doing it differently, if they have a different box or they
14 have a different method of synthesis or they don't have any
15 sterile procedures or whatever it is that they might be
16 doing entirely differently that we would have to find a way
17 for them to address.

18 MR. CONTI: So we could envision--let's just take
19 an ideal scenario where ICP holds the NDA and each site
20 could submit some supplemental information or an ANDA or
21 whatever terminology we may want to call it that would
22 either say, "We are using the exact procedure," or, "We are
23 deviating by this method; this is the justification for
24 that." This would be reviewed. You would give it your
25 blessing or whatever.

1 And the DMF also would be central within--

2 DR. BARRIO: I think that would be the easiest
3 way.

4 MS. AXELRAD: I don't know who would be a DMF or
5 just an NDA. It could be just an NDA. Maybe we don't need
6 a DMF. The ICP submits the NDA. This is what they have in
7 it. It is not like--the DMF is really when you want to keep
8 it a secret from everybody else, when you don't want anybody
9 else to see what is in the DMF but you want them to be able
10 to use it.

11 Like, for the synthesis of a bulk-drug substance
12 where the manufacturer of the bulk-drug substance doesn't
13 want anybody else to know how they make it but we have to
14 know how they make it. The drug product applicant
15 references the DMF and then we go look in the DMF and, if we
16 have questions about the synthesis, we talk to the holder of
17 the DMF.

18 The drug-product doesn't have a clue what is in
19 there except what they need to know in terms of impurities
20 in the final drug product. In this case, it is not going to
21 be done as a secret. If you are doing this for everybody,
22 it could be--

23 MR. CONTI: It should be open. And that is part
24 of the issue with the user fees. Going for a DMF would be
25 to protect that so that we can, then, sell that to recover

1 the user fees. If you eliminated the user fee from the
2 equation, then we wouldn't have to go through the DMF
3 process to have that kind of protection and it is open to
4 the public.

5 MS. AXELRAD: You could protect it in the NDA,
6 too, though. If you had to pay a user fee and you wanted to
7 charge people to access it or you had to spend money to
8 develop the NDA, you could just do the NDA and then people
9 could reference your NDA for whatever they wanted, whatever
10 you authorized them to reference it for, the chemistry, or
11 whatever.

12 MR. CONTI: The existing NDA at Peoria, would
13 there be a way to move that to ICP? Is that something that
14 we would have to negotiate with Peoria?

15 MS. AXELRAD: We would have to talk about that and
16 what we would want to do about that. I will have to find
17 out if there was some real reason why it had to come in from
18 Peoria in the first place.

19 MR. CONTI: The only reason would be is that the
20 NDA could potentially be bought. And the only way to
21 protect it for the public would be to keep it under the
22 public auspices so that the community owns it. If it is out
23 there, it is accessible to a purchaser. And then that would
24 throw the whole process in the array of the "public access."

25 MS. AXELRAD: That would have to be addressed.

1, Whoever it is, what we would want is that whoever it is that
2 acquires it has to be willing to do what is required to keep
3 the NDA updated which is submitting the supplements and the
4 annual reports.

5 MR. CONTI: That would have to be a commitment
6 that we would have to make.

7 MS. TESAR: That is a couple of weeks of work a
8 year.

9 MS. AXELRAD: We wouldn't want it transferred to
10 somebody who wasn't going to do that. And, if they don't do
11 that, we send them a notice in the Federal Register saying,
12 "We haven't gotten annual reports from you for the last five
13 years and we are withdrawing your NDA." I just signed one
14 doing that.

15 MR. CONTI: The community would, obviously, not
16 like that.

17 MS. KEPPLER: The 505(b)(2) regulations, where
18 would I find those?

19 MS. AXELRAD: There are regulations scattered in
20 314, part 314. I don't know exactly. I have to go look it
21 up and see where the (b)(2). Somewhere after 314.50, there
22 are references to (b)(2)s. But it is a very difficult
23 provision of the statute. It is not used terribly often.
24 It is more often used by a generic that wants to be
25 different than an innovator. That is the most common use of

1, it.

2 It was originally developed when there was no
3 Waxman-Hatch and there was no way to have generic drugs.
4 They wanted to sort of loosen up a little and allow people
5 to do things based on the literature.

6 After Waxman-Hatch came along, it sort of changed
7 a little bit. It incorporated the paper-NDA concept but it
8 also allowed a generic who wouldn't qualify for a generic on
9 the grounds of sameness to come in with an application that
10 addressed the difference. For example, if a generic wanted
11 an indication that wasn't approved for the innovator drug,
12 then they would submit a (b)(2) application and just submit
13 information on that indication as if there was a phantom
14 ANDA, a phantom generic, that sort of goes through into the
15 (b)(2) route.

16 It is very complicated. It looks like a generic
17 and it has to have certain patent certifications and things
18 like that has to have. We can lay that all out for you.

19 MR. CONTI: There is also a very interesting issue
20 with regard to isotopes because of patented ligands. R.K.
21 and I have talked about this in the past. This is one of
22 these issues where substituting a technetium 94 for a
23 technetium 99m on a ligand that is patented by a company
24 such as Mallinckrodt invokes a certain set of problems.

25 We have to be able to deal with that somehow

1 because now we are introducing a PET radiopharmaceutical
2 with an established ligand and how to go through that
3 process is rather formidable if it is being developed as a
4 non-proprietary drug.

5 MS. AXELRAD: That would raise a lot of difficult
6 questions, especially if you are going the (b) (2) route
7 because you would look to see if there was a patent on--I
8 don't even know if it is just the drug or the drug and its
9 components or what, but you would look.

10 They would have to look and they would have to
11 make a patent certification. If you were infringing
12 somebody's patent, that would be a definite problem. You
13 have to file a patent certification and then they can sue
14 you and challenge the fact that you are doing this. And
15 then the statute kicks in and we have to wait 30 months or
16 whatever until it is resolved in patent litigation.

17 It gets very complicated.

18 MR. CONTI: What is going to happen is a lot of
19 drugs are going to be suppressed potentially because of the
20 iodine substitutions and things like this that are going to
21 introduce PET pharmaceuticals. They could be literally not
22 available to the community because of that.

23 MS. AXELRAD: It is sort of complicated by the
24 fact that the first new chemical entity, say, for the first
25 application for ammonia, I believe, would qualify for

1, exclusivity. But would it qualify even if they didn't do
2 their own clinical trials? If it was a literature-based
3 one, would they qualify?

4 DR. LOVE: I don't think they get much if it is
5 literature. It is limited, if anything, but it is not the
6 same.

7 MS. AXELRAD: If they did something based on a
8 clinical trial, it is possible, even for a new indication
9 like single pulmonary nodules based on a new clinical trial,
10 they could get three years of exclusivity.

11 DR. LOVE: If the final approval decision required
12 that clinical trial.

13 MS. AXELRAD: If the decision on the indication
14 required a clinical trial, then they would get exclusivity
15 which would, then, block anyone else from marketing for that
16 indication.

17 DR. BARRIO: Let me go back to this FDG issue. I
18 think we envision NDAs or whatever we like to call it that
19 are much, much simpler than the NDA process we went through
20 with FDG. I still am not clear in my mind how what are we
21 going to do with the old NDA, realistically, because even if
22 the ICP takes that NDA, that NDA is probably so convoluted
23 or so difficult for everybody to comply to that something
24 has to be done to that to put it in the context of this
25 discussion that we are having in a different way, to look at

1 this and so on and so forth.

2 That is the thing I am not so sure. It is clear
3 for me, if we start from square 1, you can implement it,
4 whatever, and then we can get there. But with an existing
5 NDA that was part of the old way of thinking, that this is
6 out there, I am not so sure I really understand how we are
7 going to get there for FDG.

8 DR. LOVE: It sounds like there are two sets of
9 questions. One would be the chemistry part in relationship
10 to the old NDA and that, I think, is being taken care of
11 with the chemistry procedures that we are talking about.

12 DR. BARRIO: Then you mean we are going to cancel
13 the old procedure?

14 DR. LOVE: I am not saying it is cancelled. But I
15 am saying we are trying to develop approaches to deal with
16 the fact that manufacturing processes may be different in
17 different places, different from the old NDA, different at
18 different sites. So that, I think, we can probably take
19 care of in whatever procedures would be addressed from that
20 perspective.

21 DR. COLEMAN: So you are saying that whatever
22 procedures come about will replace whatever was in the old
23 DMF, then.

24 DR. LOVE: It would take that into consideration
25 and would address it somehow.

1 MR. CONTI: It may be an alternative.

2 DR. LOVE: As an alternative or what have you, but
3 we could address the existing manufacturing process that has
4 already been approved in the context of these procedures
5 that would be developed.

6 The other part of the question is what about this
7 other indication that has been approved, the epilepsy
8 indication? I think we could talk about that in terms of
9 what will be cross-referenced and the like.

10 MS. AXELRAD: I would say Peoria could give people
11 a right of reference to their safety and efficacy.

12 DR. LOVE: Actually, that is already in existence
13 because, when the first one came through, it was in the DMF
14 and ICP had originally decided not to claim exclusivity. So
15 that is already available for cross reference.

16 MS. AXELRAD: But not just claiming exclusivity.
17 They have to authorize a right of reference to those.

18 DR. LOVE: Exactly. But I think that that is
19 something that we can also incorporate in whatever
20 information would be addressed in terms of anyone else
21 coming in new, what they would do with the information we
22 already have as well as whatever would need to be done with
23 the existing NDA in order to get access to that particular
24 indication.

25 DR. BARRIO: Let's just say that we are ready to

1 act and say, "Well, UCLA would like to apply." What do you
2 think I should do?

3 DR. LOVE: I think that is what Jane was saying.
4 We haven't talked exactly--

5 DR. BARRIO: No, I mean in general terms, just
6 coming from the top of your head, without an existing NDA.

7 MS. AXELRAD: I will tell you what I would like
8 you to do; get a right of reference from Peoria or whoever
9 it is that owns the DMF with the safety and efficacy data
10 that says, "I give UCLA PET Center the right to reference
11 for their use in an NDA the safety and efficacy data in my
12 NDA No. so-and-so," period.

13 DR. COLEMAN: Is that in the DMF or NDA?

14 DR. LOVE: The information is in the DMF but the
15 NDA is what is approved. So Peoria would have to give us
16 the information that is relevant to their part. ICP would
17 give us authorization for whatever is relevant to your part.

18 MS. KEPPLER: My understanding is there are two
19 DMFs, a clinical and a chemistry. And the chemistry DMF has
20 been updated after the NDA was approved so that all people
21 have to be able to do is reference the two DMFs, the
22 clinical and the chemistry, currently. Somebody else might
23 know better but--

24 DR. LOVE: Some of the chemistry is actually in
25 the NDA, though, I believe; is that not correct?

1 MS. AXELRAD: I think we should check our facts,
2 but whatever it is, it would be simply a matter of getting a
3 right of reference to the chemistry and the safety and
4 efficacy data in the NDA and submitting it in whatever form--
5 -I have to deal with the issue of making sure it doesn't
6 have to be a generic.

7 We run into all kinds of problems with the
8 generic. It has to be exactly the same. That is why I say
9 it is probably going to be a (b) (2) and not a generic
10 because the strength is an issue, what was the approved
11 strength. There are a lot of issues associated with
12 sameness, and bioequivalence requirements and things like
13 that.

14 It just gets very complicated. So I would see it
15 as a (b) (2) that just has a right of reference to whatever
16 is in the--

17 DR. BARRIO: In terms of the procedure,
18 specifically?

19 MS. AXELRAD: It would be a piece of paper, or
20 pieces of paper that indicates--

21 DR. BARRIO: Just indicating that, follow that, or
22 modify, a simple--

23 MS. AXELRAD: A 356(h) form, probably. We have a
24 form that has to go with an NDA. It is a form. And then a
25 letter that explains that all of your information is coming

1 from some other sources.

2 DR. BARRIO: Then my next question is am I going,
3 or is the institution that does that going, to be subjected
4 to the same requirements of that NDA in the way it is
5 written or how the modifications will apply.

6 MS. AXELRAD: We would have to talk about that.
7 You are raising a lot of issues. We haven't gone that far
8 yet. Let's get the issues on the table. That is what we
9 need to do. We need to start the discussion so we get the
10 issues on the table.

11 DR. BARRIO: I think that NDA being there is
12 making our views a little bit not so clear in terms of what
13 it will mean for individual centers in terms of complying.

14 MR. CONTI: I think you have to make the
15 assumption that the NDA becomes a public document that is
16 held, let's say, by ICP and start from there. I think you
17 really have to go back. It has to be updated, and
18 alternatives. Unless it is eliminated completely and we
19 just start from scratch--I don't know if that is an option
20 or not--

21 DR. BARRIO: Or modified to a point so it could be
22 adapted to--

23 MS. KEPPLER: Do a 505(b)(2) for FDG as well.

24 MS. AXELRAD: You don't want to go down that
25 route. You have got that on the books. Let's not do that

1 anymore. We don't want to get rid of it. We do whatever we
2 need to modify it. We certainly don't want to get rid of
3 it.

4 DR. LOVE: Plus some of that data, as Victor was
5 saying, the safety and efficacy information in there is
6 relevant to his decisions.

7 MS. AXELRAD: Not only relevant but, probably,
8 better than what we have in terms of literature for
9 anything. So we really don't want to go down that route of
10 getting rid of it.

11 MR. WOLFANGEL: Relevant to the discussion in
12 terms of each center of filing your own NDA, I know, under
13 the '92, PDUFA, there was a requirement for a facility fee.

14 MS. AXELRAD: Establishment fee.

15 MR. WOLFANGEL: An establishment fee which was, I
16 think, \$60,000 a year. Did that carry over?

17 MS. AXELRAD: \$120,000-something a year.

18 MR. WOLFANGEL: Did that carry over to the '97
19 FDAMA?

20 MS. AXELRAD: Yes.

21 MR. WOLFANGEL: The other thing, there was an NDA
22 fee, also an annual NDA fee.

23 MS. AXELRAD: There was a product fee.

24 MR. WOLFANGEL: I am bringing those up so we have
25 an opinion discussion. You are talking about if we file an

1 NDA, you have to register as a drug manufacturing
2 establishment. There is an annual fee of at least \$60,000
3 on that. Plus, each NDA you hold, there is another fee on
4 that in addition to having to file an annual report.

5 MS. AXELRAD: No, no, no, no, no, no. That is not
6 a correct statement.

7 MR. WOLFANGEL: That is not correct?

8 MS. AXELRAD: No. First of all, what there is is
9 there is an annual establishment fee which is 120,000-some
10 dollars and there is an annual product fee which is on each
11 product. It is on each product is the way it is assessed.
12 Those are also subject to the same waiver provisions that we
13 talked about earlier. That is something we would have to
14 factor in.

15 Now, one thing we can explore--I am throwing this
16 out. We have never talked about this. I don't even know if
17 it is legal at all under the statute--is whether there would
18 have to be separate, individual applications for the
19 manufacturer site or whether there could be just one NDA and
20 seventy different manufacturer sites and information
21 submitted under the one NDA for all of those different
22 manufacturing sites.

23 MS. TESAR: Then they would have to have
24 variations.

25 MS. AXELRAD: Right. We will have to look into

1 figuring out something. I won't say it for sure, but it
2 will be an issue about the 120,000-some dollars worth of
3 establishment fees at every facility. I think we will have
4 to figure that out somehow.

5 MS. KEPPLER: To continue to clarify the fee
6 structure, if we were going to have--just so that I
7 understand it, going back to the fees by indication, the
8 \$267,000 fee for each indication, if we were going to add
9 indications for, like, FDG which would be--say, we were
10 adding three; Alzheimer's disease, tumor imaging--

11 MS. AXELRAD: It is a half.

12 MS. KEPPLER: It is a half for every additional
13 one?

14 MS. AXELRAD: If it were a supplement, if it is an
15 efficacy supplement which is a supplement for adding a new
16 indication, it is half the fee, a supplement with clinical
17 data. These would be supplements with clinical data albeit
18 literature reviews.

19 Like I said, the first one is where we would have
20 the problem with the application fee. After that, it
21 wouldn't be a new indication. It would be a 505(b)(2)
22 without a new indication and it would not pay a fee. It
23 would not be assessed a fee. It is only the first one.

24 MS. KEPPLER: Oh, okay. So every other site.

25 MS. AXELRAD: The first new indication. After

1 that, every other site would not have to pay. But the first
2 time you come in with a new indication, it is subject to an
3 application fee. But it is only half the \$250,000-some.

4 But the annual product and establishment fees are
5 issues and we will have to address those and figure out how
6 they would fare in the waiver process.

7 MR. CONTI: Ed just brought up an issue about
8 liability which is something that I think we would be
9 concerned about. Even though we all know these are
10 inherently safe species, there are possibilities of law
11 suits being generated for whatever reason, and what the
12 holder of the public NDA would be exposed to if a
13 contracting site, or subcontracting site, if that is how you
14 choose to look at it, or something like that, an entity
15 making this drug, were to have a problem.

16 MS. AXELRAD: I would like you to figure that one
17 out with your lawyers.

18 DR. COLEMAN: That may be why we went the way we
19 did, because of that.

20 MS. AXELRAD: I think we got a lot of issues on
21 the table. No solutions, but we have a lot of issues to
22 deal with.

23 MS. KEPPLER: That is good, though.

24 DR. BARRIO: I think, ideally, the paper NDA for
25 one ICP holding this is obviously the easiest way without

1, considering, of course, the legal issues. I am not sure how
2 we are going to deal with that.

3 The other thing that has been traumatic to think
4 for the PET community is the issue of the registration and
5 the registration drug manufacturers. That has been a very
6 heated issue, very complicated, emotional. In the old view
7 of the FDA, the agency wanted to see, or saw at the time,
8 that the individual PET centers were drug manufacturers. Of
9 course, we are far, far from that.

10 That concept has remained in many people's mind in
11 a negative way. If we go out there and discuss this issue,
12 or if you go and do this, you will find a very gut-related
13 opposition to that notion.

14 Is there any alternative or approach you may
15 envision that would allow us to do exactly the same thing
16 without going through the politically difficult issue of
17 registration?

18 MS. AXELRAD: We will have to look at the statute.
19 To me, drug registration means that you submit a piece of
20 paper every whatever the time is when you first get your
21 application approved and then it is at whatever frequency
22 saying that you are making PET drugs, the following PET
23 drugs, period.

24 That lets us know that you are out there doing it
25 and it gives us the right to go and inspect you against

1, whatever the requirements are. I can understand that when
2 we were considering PET to be a major manufacturing facility
3 and we were going to go out and apply 210 and 211 literally
4 to the PET facilities that that would not have set very well
5 with the community.

6 However, if we have a new, totally different set
7 of GMP requirements that we will be out looking to just see,
8 on whatever frequency we would inspect, that you are
9 complying with the set of GMP requirements that we have
10 developed that, hopefully, will be acceptable to the
11 community, that it shouldn't be a big burden.

12 MR. CONTI: As George said, this is an emotional
13 issue.

14 DR. BARRIO: It is an emotional issue.

15 MR. CONTI: Even having heard this as an emotional
16 issue, it is still not clear to me what people are objecting
17 to on this side of the table. I am still not clear in my
18 mind. I think it is in part because there are certain
19 assumptions that we have associated with that process that
20 may or may not exist in the new configuration.

21 I think, again, it is an issue of clarification
22 and communication as to what will and won't be required
23 before we say--

24 MS. AXELRAD: I hope when we have the GMP
25 discussion that the community will become more familiar and

1 there will be more understanding developed about what we are
2 going to be requiring as we have sort of been building
3 communication with regard to chemistry and with regard to
4 safety and efficacy, that, at the end of the day which is
5 when I really like to address this question, people will
6 understand that it is not such a burdensome and difficult
7 thing as it might have been had it gone into place in 1995.

8 DR. COLEMAN: I think the community has its
9 problems. That is what we heard before. They said we can
10 make it so that PET community can manufacturer the drug, can
11 compound the drugs, and will be not much different than what
12 you are doing.

13 It ends up they went in and inspected it like they
14 did, basically, a Mallinckrodt or Burroughs Wellcome or
15 whatever. The community just can't meet those standards.

16 MS. AXELRAD: Right; we know that.

17 DR. COLEMAN: The FDA had said before, well, we
18 can ease up the requirements so that PET centers can do this
19 without difficulty. You were not able to do that before.

20 MS. AXELRAD: We tried to do that but you made us
21 revoke it. We had a rule that was out that was proposing to
22 grant waivers and exceptions to GMPs which we were told to
23 revoke after we had finally got it out there to do that.

24 But, anyway, we are doing a different approach to
25 GMPs. We are doing a totally different approach to GMPs.

1, It is not going to be the same. So I think that we should
2 discuss registration sort of at the end when we have gone
3 through some of the GMP discussions and, hopefully, have
4 come to some common understanding on what those requirements
5 are going to look like because, to me, believe me, once you
6 have gone through the NDA process, the registration raises
7 many less issues or problems, I think, than trying to figure
8 out how you are going to go through the safety and efficacy
9 and lay out the chemistry and, basically, get your facility
10 into compliance with whatever GMPs you have in the first
11 place.

12 After you have done all that, registration is you
13 send us a piece of paper and we go and check, periodically,
14 as to whether you are actually meeting the GMP requirements.

15 DR. BARRIO: As you know, we produced a document
16 for your understanding of what our position is. That
17 document--I don't know, we spent a solid six months in an
18 unbelievable agonizing process of debating every single
19 possible line, believe me, of this process.

20 Almost, one way or the other, the whole community
21 participated. That was like therapy, the fact that people
22 had the opportunity to express themselves was very helpful.
23 There is absolutely no way that, in one document, we can
24 have everybody agreeing on every principle there. And, of
25 course, we didn't.

1 But, still, it is a consensus document because it
2 expresses the view of the community. This is supported by
3 SEP, SNM, ACNP for the most part. But there are certain
4 issues related to manufacturers, in individual presenters,
5 that still are of concern to a lot of people and there are
6 certain elements of that registration, for example, that is
7 probably out of proportion.

8 I don't disagree, perhaps, with the notion that it
9 may be simpler than most people think but it is not an issue
10 that you can go out and say, "Oh, guys; don't worry about
11 it. This is going to be so simple. It is a piece of
12 paper," this and that. Nobody is going to believe you.

13 MS. AXELRAD: I know.

14 DR. HOUN: But I think if the process is fairly
15 open in terms of sharing what we want to develop for new GMP
16 regulations which are different from what we would actually
17 inspect against. We would have to develop that for the FDA
18 field as well, a list of things, of all these regulations,
19 what would we actually check.

20 If we are open and having those discussions, what
21 are we going to look at, how would we evaluate it. And
22 then, what we did in mammography was we told the community,
23 "This is what we are going to look at. This is what would
24 be considered a violation. This is what would be considered
25 within normal."

1 So they knew ahead of time what the inspection
2 was. We want them to have good inspections. We don't want
3 to have problems.

4 DR. BARRIO: Don't take me wrong and don't
5 misunderstand what I am saying. We are delighted to have
6 the opportunity to discuss this and discuss all these issues
7 in a way that we never have done it before. Let's face it.
8 There is absolutely no question about that.

9 The only thing that I was referring to is that
10 there are certain items in this process of discussion, like
11 very sensitive issues. I wanted to make you aware, and
12 probably you knew it anyway--remember, we know, here, the
13 details of these discussions. Most people don't out there.

14 All this has to be explained very carefully in a
15 general context and to make sure it is explained by the
16 agency what the intent is, and very clearly say that. Don't
17 only say the percent that we have to register and leave it
18 there. We have to go and explain somehow just to make sure
19 that everybody understands that this is a very innocuous
20 mechanism and this is simply for you to know what every
21 center is doing.

22 If that is the intent, spread it out, saying that.

23 DR. HOUN: Do you have good communications with
24 most of these 70 centers?

25 DR. BARRIO: Oh, yes.

1 DR. HOUN: So, in some sense, when these things
2 get more solid to be able to give you information for you to
3 help disseminate to those other--

4 MS. KEPPLER: Right. We have already talked about
5 in terms of we have to do our own PR effort as we get down
6 the road. We have to do a PR effort to make sure that the
7 community understands why this is a great thing.

8 We are probably not going to have it be exactly as
9 we want it to be. So we realize that that is a part of what
10 we have to do. I think what George is talking about that is
11 the most difficult to deal with is the irrational fear where
12 the irrational emotional response, which is a fact--it
13 exists and we can say that it is irrational and that you
14 don't have to worry about it, but saying that almost doesn't
15 work.

16 So that is a very difficult challenge that we see
17 going forward with the community because--

18 MR. CONTI: It is perceived that there is a basis
19 for that irrational behavior.

20 MS. AXELRAD: We are going to be putting the
21 transcript of this meeting and future meetings up on the Web
22 so people will, hopefully, be able to follow the discussion.
23 I sort of hope that the people who have particular concerns
24 with what they perceive that we are going to be doing in the
25 GMP area will attend the future meetings that we are going

1 to have on GMP issues so that they can hear the discussion
2 and understand where we are coming from and how we are
3 approaching the issue.

4 MS. TESAR: We are going to be putting the
5 announcements of these meetings, the future meetings, on our
6 ICP mail and what is called PETMail which goes out to the
7 communities. So we may have more people showing up and we
8 will start that with the next meeting.

9 So once we find out from you, then we will put
10 that up on our pages and the PETMail.

11 MR. CONTI: Jane, when do you think it would be
12 reasonable to come back and visit the oncology issues? What
13 is your gut feeling on the time line for that? Maybe I
14 should ask Victor. Let me also add the reason I am saying
15 this is because of the HCFA meeting in January. I would
16 like to know a little bit more about what FDA is thinking
17 going into that town meeting.

18 MS. AXELRAD: When I heard that they were having a
19 meeting, I thought, hmmm, this is a chicken-and-egg
20 situation. I want to hear what they are going to do before
21 we do it and I'm sure people want to hear what we are going
22 to do before they do anything.

23 But they went and announced it as a public meeting
24 already.

25 MS. KEPPLER: They're first.

1 MS. AXELRAD: They get to go first.

2 MS. TESAR: Actually, our conversations with them
3 are that this is not an advisory committee meeting. It is
4 not a technical advisory committee meeting. There is not
5 going to be any information--they won't have a discussion
6 afterwards. It is just a town hall meeting to figure out
7 what the PET community is feeling.

8 We are trying to figure out why because if there
9 is not going to be a decision made as a result of this, and
10 there is not a decision--that is what we were told, there
11 are no decisions based on what we are going to be
12 presenting. So we don't know. We don't know what the
13 reason is.

14 We are happy that they are opening this up and
15 that there is going to be a dialogue again, but we really
16 don't know what is going to come out of this meeting. We
17 are going to give it our best effort and present a lot of
18 papers but we don't know.

19 MS. AXELRAD: Maybe we could do it around the HCFA
20 meeting. I said we can't, obviously, have it during the
21 HCFA meeting which is the 20th--

22 MS. TESAR: We will all be here.

23 MS. AXELRAD: Everybody will be here. Maybe we
24 could do it around the HCFA meeting?

25 DR. RACZKOWSKI: The HCFA meeting is two days.

1 MS. TESAR: The 20th and 21st.

2 MS. AXELRAD: Do you think you'll be ready?

3 DR. RACZKOWSKI: It's possible.

4 MR. CONTI: I can also tell you that it is very
5 unlikely we are going to present all that much more with
6 regard to safety and efficacy than you are seeing in front
7 of you in that literature. So the core information is at
8 hand. What we get up and say or the community gets up and
9 says will just sort of be supplemental to that.

10 MS. AXELRAD: We have to analyze it. I feel like
11 maybe we should declare whatever that week is in January
12 "PET Week" because, at the next meeting that we have, I sort
13 of envision doing the oncology indications for FDG and
14 chemistry and GMPs. So that would certainly fill up the
15 time.

16 MS. TESAR: That would help the West Coast people
17 too, though, making one trip.

18 MR. CONTI: Maybe that Monday or Tuesday, the
19 weekend after the--the town hall is what, Thursday and
20 Friday, or Wednesday or Thursday or something like that?

21 MS. AXELRAD: It is Wednesday-Thursday? Maybe we
22 could do it Monday-Tuesday. I sort of wouldn't mind doing
23 it--

24 MS. TESAR: Actually, it is a Wednesday-Thursday
25 so you could do--Martin Luther King Day is the 18th. So you

1 have got the 19th. I don't know who observes--there is the
2 19th, and then we have got the 20th and the 21st, and then
3 we have got Friday.

4 MS. AXELRAD: We could do it the 19th and the
5 22nd.

6 MS. TESAR: That is certainly around it.

7 MS. AXELRAD: I had just told Kim, "Stay away from
8 Martin Luther King week because of the holiday," but I guess
9 we are not going to do that if the HCFA meeting is that
10 week.

11 MS. TESAR: That would certainly be your goal of
12 being around the HCFA meeting.

13 MS. AXELRAD: If the HCFA meeting is just a town
14 hall meeting where they are going to be hearing from people,
15 I am not sure how helpful that would be for us because we
16 are doing a more detailed analysis. So the question is
17 really whether we will be ready to discuss the oncology
18 issues, whether we can commit now to be ready to discuss the
19 oncology indications at that time.

20 I just think it would be more efficient as long as
21 we are having you in to do chemistry and GMPs at the same
22 time. I don't care whether we do it before or after the
23 HCFA meeting. We can do one day, or half a day, or safety
24 and efficacy and then--or if we don't want to have to have
25 the chemistry people come and sit there for two days, we

1, could do one day on safety and efficacy and one day on
2 chemistry and GMPs.

3 MS. TESAR: I think that would work best for the
4 community that is going to be involved in this process. The
5 safety and efficacy people will be at the town hall meeting.

6 DR. COLEMAN: At the town hall meeting, they are
7 going to be discussing five indications; head and neck
8 cancer, colorectal, melanoma, lymphoma and brain tumor.
9 Just as Ruth was saying, it is an open meeting. Whoever
10 wants to say something can.

11 They say, talking to Mitch Burken, it is to
12 educate them on any new data not to make any decisions as to
13 what they are going to be doing.

14 MS. AXELRAD: We just got through saying that you
15 weren't looking for those kinds of specific indications that
16 you were talking about, accelerated glycolysis.

17 DR. COLEMAN: You may want to comment on that at
18 the town hall meeting, that you are supportive of that.

19 MS. AXELRAD: I'm not going to say they should
20 reimburse for it.

21 DR. COLEMAN: That is not the purpose here. The
22 purpose here, I think, is an open discussion to air issues
23 about how we feel about it. Some of those issues may
24 involve reimbursement. Some may involve the science of it.
25 I don't know what is going to happen.

1 MS. AXELRAD: Let us talk among ourselves. One of
2 the things that I want to do is talk to HCFA anyway. I want
3 them to know what we are doing here. They ought to know
4 what we are doing and we need to know a little bit about
5 what they are doing, although, frankly, I don't want to have
6 anything to do with the reimbursement side of it.

7 But we do have to at least be aware of what the
8 other group is doing so that we don't end up with a total
9 mismatch at the end of the day.

10 DR. COLEMAN: That is what we are concerned about.
11 Part of our discussion here relates to that.

12 One other comment is we have talked about GMPs. I
13 think that that term has put a bad taste in the mouth of a
14 lot of people in nuclear medicine and in PET particularly.
15 Do we have to stick with that term for what we are talking
16 about when we go to PET radiopharmaceuticals? It has got to
17 be under GMPs?

18 MS. AXELRAD: Yes, between the statute requires
19 them to be--requires any drug that is approved to be
20 manufactured in conformance with current good manufacturing
21 practices. I believe that is actually the wording in the
22 statute 505.

23 We can't invent a whole new statutory scheme here.
24 So I think we are stuck with it.

25 MR. CONTI: Are we finished?

1 DR. COLEMAN: We will get back to you our
2 recommendations for indications, the wording for the
3 cardiology, oncology, neurology. George is going to head
4 the floor with dopa outlined for you and all the review by
5 next week. Isn't that what you said?

6 DR. BARRIO: Yes; that's what I said.

7 MS. AXELRAD: We want a study-by-study analysis of
8 the data.

9 DR. COLEMAN: He's got it. No problem.

10 DR. HOUN: We will be publishing a real review of
11 not just the slides--the slides will be available on the
12 Net, but the actual medical, clinical review. I think mine,
13 now, was 50 pages. Yours is going to be, like, 300 pages.
14 So you can see how each study was looked at, how the
15 strengths and weaknesses were analyzed.

16 But, right now, that needs clearance but that
17 should be available to the public soon.

18 DR. BARRIO: At this stage of the fluoro-dopa
19 analysis, how much would you like to support your clinical
20 work or literature with extensive, actually, animal
21 literature?

22 DR. RACZKOWSKI: I would say quite a bit because I
23 think that is the basic proof of concept, so to speak, of
24 the underlying--

25 DR. LOVE: For oncology, we are talking about?

1 DR. BARRIO: No, no, no; for fluoro-dopa. That is
2 very intensive in monkeys.

3 DR. RACZKOWSKI: There are so many questions that
4 can be answered in animal models and animal data.

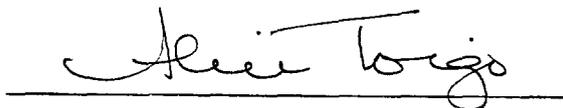
5 DR. BARRIO: Okay; good. Helpful. Then we can
6 discuss some of this data. Good. Wonderful. That makes it
7 easy because, of course, unless we are crazy we cannot do
8 certain things that we do in animals in humans. But then,
9 in animals, we have a significant amount of data
10 demonstrating cell count decrease and terminal decrease and
11 the neural-transmitter pathway. All this is extremely well
12 documented. So thank you very much for your time and
13 patience.

14 MS. AXELRAD: Thank you.

15 [Whereupon, at 3:20 p.m., the meeting was
16 adjourned.]

C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written above a horizontal line.

ALICE TOIGO

Printed by Kim Colangelo
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL **Date:** 03-Dec-1998 12:58pm
From: Kim Colangelo
COLANGELOK
Dept: HFD-160 PKLN 18B09
Tel No: 301-443-5818 FAX 301-443-9281

Subject: Overheads from Nov. 17 meeting

Good afternoon,

In order to document our Nov. 17 PET public meeting, I need copies of your overheads for the docket. Electronic copies are preferable (I have paper already). Please e-mail me your overheads if possible. If not, please let me know, and I will send the hard copies.

Thank you!
Kim

Flo ✓
Victor ✓

AGENDA

INFORMAL DISCUSSION OF LITERATURE REVIEWS OF SAFETY AND EFFICACY DATA FOR PET AMMONIA AND FDG

Tuesday, November 17, 1998
5630 Fishers Lane, Room 1066, Rockville, MD

Participants (see attached)

Moderator: Jane Axelrad, Associate Director for Policy,
Center for Drug Evaluation and Research

Opening Remarks from FDA	Jane Axelrad
Opening Remarks from the Institute for Clinical PET	Jorge Barrio
Background	Patricia Love
Presentation of PET Ammonia Literature Review	Florence Houn
Discussion of PET Ammonia Literature Review	
Presentation of PET FDG Literature Review	Victor Raczkowski
Discussion of PET FDG Literature Review	
Summary Discussion and Closing Remarks	

PARTICIPANTS

INFORMAL DISCUSSION OF LITERATURE REVIEWS OF SAFETY AND EFFICACY DATA FOR PET AMMONIA AND FDG

INSTITUTE FOR CLINICAL PET

Jorge Barrio, PhD, Professor, Department of Molecular and Medical Pharmacology, University of California – Los Angeles

R. Edward Coleman, MD, Professor of Radiology,
Duke University Medical Center

Peter S. Conti, MD, PhD, Associate Professor of Radiology, Clinical Pharmacy, and Biomedical Engineering, University of Southern California

Jennifer Keppler, Executive Director, Institute for Clinical PET

Ruth Dean Tesar, Vice President and General Manager,
PETNet Pharmaceutical Services, LLC

FOOD AND DRUG ADMINISTRATION- CENTER FOR DRUG EVALUATION AND RESEARCH

Jane Axelrad, Associate Director for Policy

Florence Houn, MD, MPH, Deputy Director, Office of Drug Evaluation II

Patricia Love, MD, Director, Division of Medical Imaging and Radiopharmaceutical Drug Products, Office of Drug Evaluation III

Victor Raczkowski, MD, Deputy Director, Office of Drug Evaluation III

Key Aspects of Study Protocol and Reports

- ◆ Defined Clinical Setting
- ◆ Selection of Subjects
- ◆ Image Evaluations
- ◆ Truth Standards
- ◆ Controls
- ◆ Endpoints
- ◆ Analytic Plan
- ◆ Indication Considerations

Focus

- ◆ Clinical Safety and Efficacy of Commonly Used PET Drugs
 - FDG and Ammonia Models
 - Use of Published Literature Alone
 - Support from Pharmacology-Toxicology, Pharmacokinetics, Pharmacodynamics

Developing Medical Imaging Drugs and Biologics - Draft

◆ Indications

- Structure Delineation
- Functional, physiological or biochemical assessment
- Disease or pathology detection or assessment
- Diagnostic or therapeutic patient management

Developing Medical Imaging Drugs and Biologics - Draft

- ◆ Comment period closes December 14, 1998

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GUIDANCE FOR INDUSTRY - Draft

Developing Medical Imaging
Drugs and Biologics

“Radiopharmaceuticals” Proposed Rule

- ◆ Indications
- ◆ Evaluation of Effectiveness
- ◆ Evaluation of Safety
 - Radiation Dose; Toxicology; Adverse Events
 - Risk of an incorrect diagnostic determination
 - Results of human experience with other uses

“Radiopharmaceutical” - Proposed Rule

- ◆ Intended for use in the diagnosis of a disease or a manifestation of a disease in humans
- ◆ Spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons
- ◆ Nonradioactive reagent or nuclide generator that is intended to be used in the preparation of such article

Proposed Rule - In Vivo
Radiopharmaceuticals Used for
Diagnosis and Monitoring

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Published Literature Alone

- ◆ Robust results from prospective analyses
(not post hoc special analyses)
- ◆ Conducted by credible groups with properly documented operating procedures

Published Literature Alone

- ◆ Multiple studies conducted by different investigators; adequate designs; consistent results
- ◆ High level of detail (statistical/analytic plan, accounting of patients)
- ◆ Appropriately objective endpoints

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GUIDANCE FOR INDUSTRY

Providing Clinical Evidence of
Effectiveness for Human Drug and
Biologic Products

PET Radiopharmaceutical Approval Procedures - Ongoing

- ◆ Potentially Useful Documents
 - Guidance; Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products
 - Radiopharmaceutical Proposed Rule
 - Draft Guidance; Developing Medical Imaging Drugs and Biologics

Different Options Under Consideration

- ◆ CMC and Microbiology - Ongoing
- ◆ Clinical Safety and Efficacy of Commonly Used PET Drugs
 - FDG and Ammonia Models
 - Use of Published Literature Alone
 - FDA Review Primary Articles and Develop Database

Labeling

- ◆ Useful information
 - Indication
 - Summary of Critical Studies
 - Dosing & Administration
 - Adverse Events
 - Clinical Pharmacology
 - Special Population Issues

Clinical Section

- ◆ Phase 1 - safety in humans (normal volunteers or patients); dose ranging
- ◆ Phase 2 - preliminary efficacy data; dose finding; developing hypothesis; additional safety data
- ◆ Phase 3 - confirmation of hypothesis; expansion of safety database

Introduction

- ◆ Objective
- ◆ Background
- ◆ Potentially Useful Documents
 - In Vivo Radiopharmaceutical Proposed Rule
 - Industry Guidances
- ◆ Options

N-13 Ammonia PET: Safety and Effectiveness Review

Florence Houn MD MPH

Sonia Castillo PhD

November 17, 1998

N-13 Ammonia Team

- Sonia Castillo- Stat
- Kaye Cho- PM
- Flo Houn- Medical
- David Hussong- Micro
- Ravi Kasliwal- Chem
- Adebayo Laniyonu- Pharm/Tox
- David Udo- Biopharm

N-13 Ammonia S&E Review

Conclusions

- Effectiveness
 - To assess myocardial perfusion
- Safety
 - Single doses up to 25 mCi studied
 - 2 IV doses up to 20 mCi each studied

N-13 Ammonia S&E Review

- Guidances on Clinical Effectiveness/Medical Imaging
- Intended Use of N-13 Ammonia
- External Standards
- Search Methodology
- Selection Criteria
- Review of Findings
- Conclusions

N-13 Ammonia S&E Review

Guidance on Clinical Effectiveness-Use of Published Literature Alone

- Multiple studies/adequate design/consistent findings
- Detailed protocol
- Objective and appropriate endpoints
- Consistent conclusions of efficacy
- Conduct of studies with documented operating procedures
- Examples: secretin, bleomycin and talc, doxycyline

N-13 Ammonia S&E Review

Adequate/Well-Controlled (Med. Imaging Guidance)

- Selection of subjects=Target population
- Readers: independent, masked, randomized, separate
- Standards of truth
- Endpoints
- Analysis plans
- Safety: toxicity and radiation assessment

N-13 Ammonia S&E Review

Intended Use: To assess Myocardial Perfusion (MP)

- Preliminary review for major uses
- “Developing Medical Imaging Drugs and Biologics” draft guidance
 - “Functional, Physiological, or Biochemical Assessment”
 - Validated to a standard of truth
 - Spectrum of disease and normality tested
 - Pharmacological basis of “functional claim”

N-13 Ammonia PET

External Standards for MP

- Vessel Anatomy, CAD, and blood flow
 - Coronary Angiography
 - Rubidium-82
- Coronary microperfusion
 - Functional Aspects
 - Wall Motion
 - Functional Capacity (stress testing)
 - Clinical outcomes (survival)

N-13 Ammonia PET

Literature Search Methodology

- Criteria for Search
 - January 1, 1990 to July 1, 1998
 - Human clinical trials
 - English
 - On-line databases: Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts, and Embase
 - PET community suggested articles
 - References cited in above articles

N-13 Ammonia PET Literature Search Methodology

- Selection Criteria
 - N-13 ammonia PET results compared to appropriate clinical standard of truth
 - Relevant study question to MBP
 - Well-described study population
 - Procedures to reduce bias

N-13 Ammonia S&E Review

Published Literature

- Adequate/Well-Controlled Clinical Trials (2)
 - Prospective enrollment - Study Hypothesis related to intended use
 - Study population similar to target population for clinical use
- Other Controlled Published Studies (3)
 - Various study hypotheses
 - Retrospectively selected patients; normal volunteers assumed CAD-free
- Other Published Studies (9)
 - Wide variety of study hypotheses
- MBF Quantification Algorithm (3)

N-13 Ammonia S&E Review

Adequate/Well-Controlled Studies

- Gould LK, Goldstein RA, Mullani NA, et al. J Am Coll Cardiol 1986;7:775-89.
- Demer LL, Gould LK, Goldstein RA, et al. Circulation 1989;79:825-35.

N-13 Ammonia S&E Review

Other Controlled Studies

- Schelbert HR, Wisenberg G, Phelps M et al Am J Cardiol 1982;49:1197-1207.
- Di Carli M, Sherman T, Khanna S et al. J Am Coll Cardiol 1994;23:860-68.
- Gewirtz H, Fischman AJ, Abraham S et al. J Am Coll Cardiol 1994;23:851-59.

N-13 Ammonia S&E Review

Other Supportive Studies

- Beansland RSB, Muzik O, Melon P, et al. J Am Coll Cardio 1995;26:1465-75.
- Czernin J, Barnard RJ, Sun KT, et al. Circulation 1995;92:197-204.
- Di Carli MF, Davidson M, Little R, et al. Am J Cardiol 1994;73:527-33.
- Gould LK, Martucci JP, Goldberg DI, et al. Circulation 1994;89:1530-38.
- Gould LK, Ornish D, Scherwitz L, et al. JAMA 1995;274:894-901.

N-13 Ammonia S&E Review

Other Supportive Studies

- Haas F, Haehnel CJ, Picker W, et al. J Am Coll Cardiol 1997;30:1693-1700.
- Laubenbacher C, Rothley J, Sitomer J, et al. J Nucl Med 1993;34:968-978.
- Sambucetti G, Parodi O, Giorgetti A, et al. J Am Coll Cardiol 1995;26:615-23.
- Soufer R, Dey HM, Lawson AJ, et al. J Nucl Med 1995;36:180-87.

N-13 Ammonia S&E Review

MP Quantification Algorithm

- Krivokapick J, Smith GT, Huang SC, et al. Circulation 1989;80:1328-37.
- Hutchins GD, Schwaiger M, Rosenspire KC, et al. J Am Col Cardiol 1990;15:1032-42.
- Gerwitz H, Skopicki HA, Abraham SA, et al. Cardiology 1997;88:62-70.

N-13 Ammonia S&E Review

Adequate /Well-Controlled: Gould (1986)/Demer (1989)

- Objective: Feasibility study for diagnosing CAD with Rb/NH₃ using rest/stress testing
- Sample size: 23/50 patients received NH₃
- Design: Prospective; compared angio and PET
- Image Protocol: Masked, Reread x 3
- Dose: 2 IV 10-20 mCi N-13 ammonia or 30-50 mCi Rubidium
- Significant CFR defined <3.0 on angio; % isocount reduction assumed proportional to % decrease CFR
- Sensitivity 21/22 (95%)
Specificity 9/9 (100%)

N-13 Ammonia S&E Review

Adequate/Well-Controlled: Demer (1989)

- Objective: Accuracy of N-13 NH₃ in evaluating CAD using rest/stress testing compared to coronary angiography
- Sample Size: 111/193 pts received N-13 NH₃ (n=174 analyzed)
- Inclusion Criteria: All patients undergoing cath (population suspect for disease but some do not have it).
- Design: Compare stenosis flow reserve (SFR-automated) vs. PET defect scores

N-13 Ammonia S&E Review:

Adequate and Well-Controlled: Demer (1989)

- Scales: SFR 0-5 (5=nl;<3=signif. CAD) PET defect scores 0-5 (5=severe perfusion defect;>2 signif. CAD, SFR<3)
- Image Protocol: masked, independent, reread x 2, rest/stress read side by side
- Scores for PET averaged, interobs. variation defined and tracked, dispute resolution described
- Dose: 2 IV 10-20 mCi NH₃ / 30-50 mCi Rb

N-13 Ammonia Review: Demer (1989) Con't.

- Results

- Spearman Correlation Coefficient 0.77 (± 0.06) for patients' scores of most severe PET/SFR scores
- Rb/NH3: For N=193, 2 false positives (1 Rb/1NH3); 7 false neg (2 Rb/5 NH3)

N-13 Ammonia S&E Review

Demer (1989) 2x2 Table (Patients)

	SFR < 3	SFR ≥ 3	Totals
PET Score ≥ 2	94	12	106
PET Score < 2	2	66	68
Totals	96	78	174

N-13 Ammonia S&E Review Demer (1989) Con't.

- Results Continued
 - Figure 3
 - FDA approach to calculating sensitivity and specificity

N-13 Ammonia S&E Review Demer (1989) Con't.

- See Overhead of Figure 3

N-13 Ammonia S&E Review

Demer (1989) 2x2 Table (Vessels)

	SFR < 3	SFR ≥ 3	Totals
PET Score ≥ 2	133	28	161
PET Score < 2	2	80	82
Totals	135	108	243

N-13 Ammonia S&E Review

Demer (1989) Sensitivity/Specificity

- Patients
 - Sens=98% (95% CI: 92.1-99.7%)
 - Sp=85% (95% CI: 74.7-91.7%)
- Vessels
 - Sens=99% (95% CI: 94.9-99.9%)
 - Sp=74% (95% CI: 64.5-81.7%)

N-13 Ammonia S&E Review Demer (1989)

- Strengths
 - Inclusion criteria
 - Continuous endpoints for SFR/PET severity
 - Images read by 2 readers, independently, masked
 - Interobserver differences in PET tracked/analyzed
 - Graphical data to calculate sens/sp

N-13 Ammonia S&E Review Demer (1989) Con't.

- Strengths Continued
 - Dispute resolution
 - Detailed information on readers' performances
 - Detailed information on reader variability
 - Use of SFR for coronary perfusion from angio
 - Large number of patients

N-13 Ammonia S&E Review Demer (1989) Con't.

- Weaknesses
 - Rubidium/NH₃
 - Age/Sex distribution
 - 19 patients excluded from analysis “because they had undergone revascularization during acute infarction causing residual stenosis severity that would not be comparable to the severity of the fixed perfusion defect.”

N-13 Ammonia S&E Review

Other Controlled Studies

- **Schelbert (1982)**
- Objective: Correlate angio and N-13 ammonia PET.
- Sample Size: N=32 CAD/ N=13 normal volunteers.
- Design: PET compared to angio. 11CAD pts stress-thall.
- Image Protocol: 2 readers (consensus), masked, agreement tracked
- Dose: 2 IV doses of 0.22 ± 0.09 mCi
- Results: **Sens (>50% stenosis) was 97% (31/32 patients).**
Sp assumed as 100% (0/13). Thallium identified 11/19 stenosed vessels versus 17 PET+/19 stenoses vessels.

N-13 Ammonia S&E Review

Other Controlled Studies

- **Di Carli (1994)**
- Objective: Relationship of collateral flow, wall motion, and viability (defined by metabolism of 18-FDG).
- Sample Size: N=42 cons. patients (78 vessels) w/ CAD (angio) and LV dysfunction
- Design: Comparison
- Image Protocol: PET semiquant., 2 observers (consensus)
- Dose: 20 mCi
- Results: 58% w/angio collaterals had ↓ N-13 flow; 50% w/no angio collaterals had N-13 flow.

N-13 Ammonia S&E Review

Other Controlled Studies

- **Gerwitz (1994)**
- Objective: Determine minimum level of MP.
- Sample Size: N=26 pts with chronic MI referred for thall and PET.
- Design: Comparison of wall motion and PET FDG/NH₃
- Image Protocol: Quantified PET readings; Visual analysis for Ventriculography, echocardiograms
- Dose: 25 mCi NH₃/7.5 mCi FDG
- Results: Perfusion correlates with wall motion. Results demonstrate biologic consistency.

N-13 Ammonia Review: Other Published Studies

Study	Obj.	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Beanlands (1995)	To study MBF reserve and angio	N=5 vol. N=7 vol. mid-aged N=15 CAD on angio	Correlation of results	Quantit.	2 IV doses of 20 mCi	R=0.75 (min lumen diameter) R= -0.56 (%area sten)
Czernin (1995)	To study MP response to conditioning	N=13 vol. 4/13 CAD N=8 nr/nc Controls	Intervention; Assess exercise Capacity	Semiquant.	2 IV doses of 10-15 mCi	Improved flow and cardiac endpts.
Di Carli (1994)	To predict survival using PET/angio	N=93 consec. pts. w/severe LVdysfun.	Survival; F/U avg 13.6 mons (2-31mons)	Semiquant. 2 obs. Masked Independ.	20 mCi	Supports microperfusion use of PET.

N-13 Ammonia Review: Other Published Studies

Study	Obj.	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Gould (1994)	To assess perfusion after chol program	N=15 CAD	Rand. to 3 program; control-Rx-control sequential trial.	Quanti.	2 IV doses of 18 mCi	PET correl. w/lower chol/better exercise capacity
Gould (1995)	To assess CAD with angio and PET pre/post risk modif.	N=20 active N=15 usual care	Rand. Controlled trial	Quanti. at initial and 5 yrs	18 mCi NH3 or 40-50 mCi Rb	Correlation of PET and angio results
Haas (1997)	To assess PET's correl. w/ outcomes CABG decisions	N=76 pts w/3VD	Survival study; use of PET data on outcomes	Semi-quant.	740 MBq (20 mCi)	PET results affected CABG selection—survival > angio

N-13 Ammonia Review: Other Published Studies

Study	Objective	Sample Size	Design	Image Protocol	Dose	Safety/ Efficacy
Laubenbacher (1993)	To evaluate automated analysis for 3-D MBF	N=29 CAD (angio) N=23 controls	Compare angio-PET; ROC	2 readers masked vs. Quanti. Vari. Eval.	2 IV doses of 740 MBq (20 mCi)	Agreement of software and observers
Sambucetti (1995)	To study MP in collaterals	N=19 pts w/CAD N=13 nl	Compare angio and PET	Quanti.	2 IV doses of 0.2 mCi/kg	Angio and PET results give diff collat. info
Soufer (1995)	To study reverse redist. in Thallium	N=32 pts with CAD and RR	Compare PET/wall motion/thal -F/U14mon	Quanti.	15 mCi	Contributes info on PET/wall-motion/ micro-perf

N-13 Ammonia S&E Review

Weaknesses of Literature

- Absence of statistical criteria for significance and power
- Small numbers of subjects
- Absence of source data
- Bias (publication bias, subjectivity of readers scoring, patient selection)

N-13 Ammonia PET Review

Conclusions

- Efficacy
 - Intended Use: To assess myocardial perfusion
 - Consistent findings, diverse populations
 - Sensitivity and specificity calculated
 - Blood flow and microperfusion

N-13 Ammonia S&E Review

Conclusions

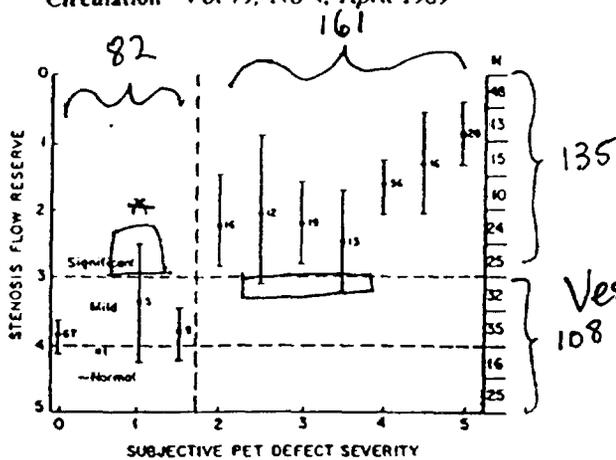
- Safety (Ammonia/Radiation)
 - Small amount of NH₃ introduced
 - Know metabolism and excretion
 - Short physical half-life (10 minutes)
 - Acceptable radiation dosimetry
 - Acceptable risk of radiation

N-13 Ammonia S&E Review

Conclusions

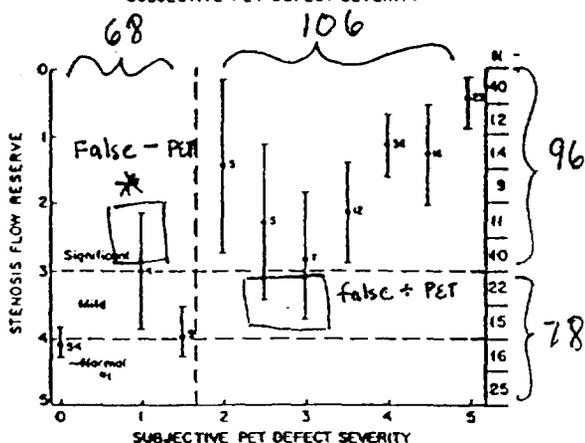
- Effectiveness:
 - **To assess myocardial perfusion**
- Safety:
 - **Single doses of up to 25 mCi studied**
 - **2 IV doses up to 20 mCi each studied**

* 2/5 assigned
SFR > 3 by FDA



Vessels n=243

* 2/4 assigned
SFR > 3 by FDA



Patients n=174

FIGURE 3. Top panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in the corresponding anatomic region for 243 stenoses. Mean value of SFR is plotted as a function of PET defect severity. The horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses. The error bars represent 90% confidence intervals. The number of patients represented is shown adjacent to each point. Right-hand column lists the numbers of patients found in each interval of SFR, to illustrate the distribution of coronary disease in this population. SFR is plotted on a reverse scale (5 to 0) to parallel stenosis severity. No error bars are shown for the point representing a single stenosis. Bottom panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in 174 patients. The most severe stenosis was compared with the most severe PET defect for each patient. Nineteen patients with revascularization during acute infarction were excluded because the residual stenosis severity would not be comparable to the severity of the fixed perfusion defect. As for the top panel, the horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses.

F-18 FDG Cardiac PET
Clinical and Statistical Review
Preliminary Findings

Victor FC Raczkowski, MD MS

Mahboob Sobhan, PhD

F-18 FDG Team

- M Sobhan-Stat
- R Jordan-PM
- V Raczkowski-Clin
- D Hussong-Micro
- R Kasliwal-Chem
- A Laniyonu-Pharm/Tox
- A Sancho-Biopharm

F-18 FDG Cardiac PET Clin/Stat Review Preliminary Conclusions

- Efficacy
 - To identify “viable” myocardium
- Safety
 - Previous NDA: Doses up to 10.5 mCi studied
 - Most Literature: Doses up to 10 mCi studied

F-18 FDG PET

Results of Literature Search

<u>Database</u>	<u>Number of References</u>
Medline	250
Embase	274
Derwent	38
Cochrane	33
Cancerlit	25
Biosis	9
HSTAR	3

F-18 FDG Cardiac PET

Framework for Literature Review

- Draft Guidance for Industry: “Developing Medical Imaging Drugs and Biologics”
 - Federal Register Notice of Availability
63 FR 55067
 - Internet
<http://www.fda.gov/cder/guidance/index.htm>

F-18 FDG Cardiac PET

Framework for Literature Review

Consideration of Potential Claims:

- Structure delineation
- Functional, Physiological, or Biochemical Assessment
- Disease or Pathology Detection or Assessment
- Diagnostic or Therapeutic Patient Management
- Multiple Claims
- Other Claims

F-18 FDG Cardiac PET

Framework for Literature Review

- Validity of information provided by F-18 FDG Cardiac PET
 - Appropriate truth standards in studies, and/or;
 - Contribution to beneficial patient outcomes
- Potential clinical usefulness of information

F-18 FDG Cardiac PET

Framework for Literature Review

- Sufficient detail of study design, study population, doses used, endpoints, image acquisition, image interpretation, statistical analyses, etc.
- Study population sufficiently similar to the population for which F-18 FDG is intended
- Procedures to reduce potential bias: e.g., blinded image evaluations, randomization

F-18 FDG Cardiac PET

Initial Literature Selection

- Baer FM, Voth E, Deutsch HF, et al. J Am Coll Cardiol 1996;28:60-9.
- Carrel T, Jenni R, Haubold-Reuter S, et al. Eur J Cardio-Thorac Surg 1992;6:479-84.*
- Gerber BL, Vanoverschelde JJ, Bol A, et al. Circulation 1996;94:651-9.

F-18 FDG Cardiac PET

Initial Literature Selection

- Gropler RJ, Geltman EM, Sampathkumaran K, et al. J Am Coll Cardiol 1993;22:1587-97.
- Knuuti MJ, Saraste M, Nuutila P, et al. Am Heart J 1994;127:785-96.
- Lucignani G, Paolini G, Landoni C, et al. Eur J Nucl Med 1992;19:874-81.*

F-18 FDG Cardiac PET

Initial Literature Selection

- Maes AF, Borgers M, Flameng W, et al. J Am Coll Cardiol 1997;29:62-8.
- Marwick TH, MacIntyre WJ, Lafont A, et al. Circulation 1992;85:1347-53.
- Tamaki N, Yonekura Y, Yamashita K, et al. Am J Cardiol 1989;64:860-5.*

F-18 FDG Cardiac PET

Literature Selection

- Tamaki N, Ohtani H, Yamashita K, et al. J Nucl Med 1991;32:673-8.*
- Tamaki N, Kawamoto M, Tadamura E, et al. Circulation 1995;91:1697-705
- Tillisch J, Brunken R, Marshall R, et al. N Engl J Med 1986;314:884-8.*

F-18 FDG Cardiac PET

Carrel et al.

- Objective: Post-op assessment of systolic and diastolic LV function after CABG
- Design: Prospective; Pre-CABG ^{82}Rb and ^{18}FDG ; Pre- and post CABG 2-D Echo
- Subjects: n=23, CAD, LVEF<45%, pre-CABG
- Segments: One segment per subject analyzed. MM=19; Match=4
- Dose: Not in text
- Endpoints: LVEF, global and regional wall motion, diastolic relaxation, NYHA functional class
- Image evaluations: Not specified if PET and 2-D echo readings were blinded

F-18 FDG Cardiac PET

Carrel et al.

- Results:
 - LVEF: Significant increase at rest (from 34% to 52%).
Significant increase during exercise (from 31% to 58%)
 - Wall motion: No change in overall segmental wall motion score. Functional improvement in 16/19 (84.3%) segments with mismatch, and 1/4 segments (25%) with match.
 - Diastolic relaxation: Significant reduction in time constant of diastolic relaxation.
 - NYHA Class: Nearly all patients improved

F-18 FDG Cardiac PET

Carrel et al.

- Strengths (not all inclusive)
 - Prospective
 - Evaluated a range of outcomes: regional LV function, global LV function, clinical outcomes (NYHA functional class)
 - 2-D echo evaluations performed at more than one time point (7 days and 3 months after surgery)
 - Graft patency was assessed post-operatively

F-18 FDG Cardiac PET

Carrel et al.

- Weaknesses (not all inclusive)
 - Small Sample Size
 - PET and 2-D Echo images probably not read blindly
 - Incomplete evaluation of segments (only one per patient)
 - In wall motion analyses: unclear if, or how, 2-D Echo images were aligned with PET images to ensure that corresponding segments were being evaluated

F-18 FDG Cardiac PET

Carrel et al.

- Weaknesses (not all inclusive)
 - Postoperative PET not performed
 - Doses, PET protocol, glucose-loading, etc. not specified in manuscript, but presumably in reference. Reference (in German) not readily available.

F-18 FDG Cardiac PET

Marwick et al.

- Objective: Evaluate metabolic response of hibernating tissue to revascularization
- Design: Pre- and post-CABG rest-stress (dipyridamole) ^{82}Rb , post-exercise ^{18}F FDG, and digitized 2-D echo
- Subjects: n=16, fasting, previous MI, no diabetes,
- Segments: 85 segments pre-op with perfusion and wall-motion disturbances
- Dose: 4-10 mCi ^{18}F FDG
- Endpoints: Wall motion, ^{82}Rb “perfusion,” ^{18}F FDG activity
- Image evaluations: Two blinded readers for ^{82}Rb PET, ^{18}F FDG PET, and 2-D echo

F-18 FDG Cardiac PET

Marwick et al.

- Results:
 - pre-op: 85 segments identified with fixed perfusion defects and resting wall motion disturbances
 - post-op: 35 (41%) classified as hibernating, 50 (59%) as non-hibernating

F-18 FDG Cardiac PET

Marwick et al.

- Hibernating segments (n=35)
 - Significant improvement in wall motion, increase in perfusion, and decrease in (super-normal) ^{18}F FDG activity (comparing post-CABG to pre-CABG)
 - 10 segments still had abnormally high ^{18}F FDG activity
 - 25 (71%) were correctly predicted to be viable by FDG criteria

F-18 FDG Cardiac PET

Marwick et al.

- Nonhibernating segments (n=50)
 - No significant difference in wall motion or perfusion (comparing post-CABG to pre-CABG).
 - Significant decrease in (super-normal) ^{18}F FDG activity (Comparing post-CABG to pre-CABG)
 - 38 (76%) were correctly predicted to be nonviable by FDG criteria

F-18 FDG Cardiac PET

Marwick et al.

- Strengths (not all inclusive)
 - Blinded image evaluations
 - PET performed pre-op and post-op
 - Image alignment:
 - PET with PET: ^{82}Rb and ^{18}F FDG scans performed in same position; ^{82}Rb and ^{18}F FDG images superimposed
 - Echo with PET: Defined segments of myocardium that were comparable to those obtained with the other imaging modality

F-18 FDG Cardiac PET

Marwick et al.

- Weaknesses (not all inclusive)
 - Small sample size
 - Endpoints evaluated at only one time point after CABG
 - Determination of whether segments were hibernating was done retrospectively (i.e., hibernation was not predicted prospectively)
 - Sickest patients excluded from protocol (e.g., no three-vessel disease).

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Objective: Assess the clinical value of PET in the evaluation of CABG
- Design: $^{13}\text{NH}_3$, ^{18}FDG , and radionuclide ventriculography (RNV) pre- and post-CABG
- Subjects: n=22, fasting, undergoing CABG
- Segments: 51 segments with pre-CABG perfusion defect; 46 segments with pre-CABG wall motion abnormalities
- Dose: 2-7 mCi ^{18}FDG
- Endpoints: Wall motion, Perfusion
- Image evaluations: 3 non-blinded readers for PET scans; 3 blinded readers for RNV

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Results

- Wall Motion

46 segments with abnormal pre-CABG perfusion:

- 23 segments predicted to be ischemic. Wall motion improved in 18 (78%) of these segments.
- 23 segments predicted to be scar. Wall motion improved in 5 (22%) of these segments.
- Predictive accuracy of PET for wall-motion improvement is 78% for ischemic segments and 78% for scarred segments ($p < 0.001$).

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Wall Motion (cont):
 - 19 asynergic segments had increased FDG uptake before CABG.
 - Of these 19 segments
 - decrease in ^{18}F FDG uptake in 13 (68%) after CABG, all of which showed improvement in asynergy
 - persistent ^{18}F FDG uptake in 6 (32%) after CABG, half of which showed improvement in asynergy ($p < 0.01$)

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Wall Motion (cont):
 - In contrast, 4 out of 5 segments (80%) showing new FDG uptake after CABG had further wall motion abnormalities

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Results

- Perfusion

- 51 segments with abnormal pre-CABG perfusion:

- 21 segments predicted to be ischemic. Perfusion improved in 13 (62%) of these segments.
 - 30 segments predicted to be scar. Perfusion improved in 8 (27%) of these segments.
 - Predictive accuracy of PET for perfusion improvement is 62% for ischemic segments and 73% for scarred segments ($p < 0.05$).

F-18 FDG Cardiac PET

Tamaki et al. (1989)

- Strengths (not all inclusive)
 - Multiple blinded readers for radionuclide ventriculography (evaluation of wall motion)
 - PET scans performed both before and after CABG
 - Multiple readers for PET scans
- Weaknesses (not all inclusive)
 - Small sample size
 - Readers of PET scans were not blinded

F-18 FDG Cardiac PET

Tillisch et al.

- Objective: To determine if ^{18}F FDG uptake in segments with abnormal motion indicates viability, and if uptake predicts functional recovery
- Design: ^{13}N NH_3 and ^{18}F FDG pre-CABG; Contrast or radionuclide ventriculography pre- and post-CABG; subset ^{201}Tl
- Subjects: n=17, resting wall-motion abnormality, pre-CABG, glucose loaded
- Segments: 73 segments with abnormal wall motion pre-CABG

F-18 FDG Cardiac PET

Tillisch et al.

- Dose: 10 mCi ^{18}F FDG
- Endpoints: Wall motion, ejection fraction
- Image evaluations: Three blinded readers for contrast and radionuclide ventriculograms.
- Image evaluations (cont): PET images evaluated quantitatively, and counts in each sector compared to normal values for each sector. PET images reconstructed and correlated with ventriculograms to ensure regional concordance

F-18 FDG Cardiac PET

Tillisch et al.

- Results

Of 73 segments with abnormal wall motion:

- 46 segments predicted to be reversible. Five excluded because of inadequate revascularization. 41 segments analyzed.
- 27 segments predicted to be irreversible. One excluded because of inadequate revascularization. 26 segments analyzed.

F-18 FDG Cardiac PET

Tillisch et al.

- Abnormal wall motion (AWM)
 - Reversible segments
AWM in 35 of 41 segments correctly predicted by PET to be reversible (85% predictive accuracy)
 - Irreversible segment
AWM in 24 of 26 segments correctly predicted by PET to be irreversible (92% predictive accuracy)
 - No difference in mean wall-motion score after the operation compared to score before the operation

F-18 FDG Cardiac PET

Tillisch et al.

- Ejection Fraction
 - Mean LVEF increased significantly in the study population from 32% (before the operation) to 41% afterward
 - In 11 patients, resting wall motion improved postoperatively in two or more regions. Mean LVEF increased from 30% (before the operation) to 45% afterward in this group.

F-18 FDG Cardiac PET

Tillisch et al.

- Strengths (not all inclusive):
 - Blinded image evaluation of contrast and radionuclide ventriculograms
 - Quantitative evaluation of PET images may be less prone to possible bias
 - To increase segmental concordance, regions on contrast or radionuclide ventriculograms were correlated with reconstructed PET scans

F-18 FDG Cardiac PET

Tillisch et al.

- Weaknesses (not all inclusive):
 - Small sample size
 - Attempt was made to assess whether adequate revascularization of an abnormally contracting region was achieved, but this was not confirmed routinely by postoperative angiography. Improvements in wall motion may be due to factors other than satisfactory revascularization.

F-18 FDG Cardiac PET European Multicenter Study

- Abstract:

Louvain B, Lyon F, Groningen NL et al.
Predictive Value of FDG Imaging in 502
Patients with Chronic Ischaemic Left
Ventricular Dysfunction Enrolled in a
Prospective European Multicentre Viability
Study. Heart 1996;75(5):P68

F-18 FDG Cardiac PET

European Multicenter Study

- Objective: To ascertain the value of quantitative ^{18}F FDG PET to identify chronically dysfunctional LV segments whose function improve after coronary revascularization.
- Interim analysis: Complete follow-up on 105 patients
- Notable Design Features
 - Multicenter
 - Prospective
 - Euglycemic hyperinsulinemic clamp
 - Endpoints include LVEF and Regional wall motion

F-18 FDG PET Literature Search

- Search Criteria for all Uses
 - January 1, 1990 to July 1, 1998
 - Human clinical trials
 - English
 - Medline, Embase, Cochrane Controlled Trials Register, Cancerlit, Derwent Drug File, HSTAR, Biosis Previews, International Pharmacology Abstracts
 - Articles provided by PET community
 - References cited in above articles
 - Cardiac: References in ACC/AHA Guidelines, USPDI

F-18 FDG Cardiac PET

Preliminary Conclusions

- Efficacy
 - Efficacy supported by basic pharmacology
 - Any dosimetry/pharmacokinetic data in diabetics? renally impaired?
 - F-18 FDG may identify “viable” myocardium
- Safety
 - Prior NDA data (cardiac patients any different?)
 - No evidence that it was even considered in most journal articles

Guidance for Industry

Developing Medical Imaging Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, or from the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>. Copies also can be obtained by fax from 1-888-CBERFAX or 301-827-3844 or by mail from the Voice Information System at 800-835-4709 or 301-827-1800.

For questions on the content of the draft document contact (CDER) Robert K. Leedham Jr., 301-443-3500; or (CBER) George Q. Mills 301-827-5097.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
October 1998
Clin #

(3) If it cannot be determined that the fasteners are correctly installed with wet sealant, remove and inspect the specified number of additional fasteners in that zone, oversize the holes, apply primer, and install new, oversize fasteners with wet sealant, in accordance with the alert service bulletin.

(i) If, after removal, all additional fasteners inspected in that zone are found to be correctly installed with wet sealant, no further action is required for that zone.

(ii) If, after removal, the fasteners in that zone are found to be incorrectly installed, remove all other fasteners in the zone, oversize the holes, apply primer, and install new, oversize fasteners with wet sealant, in accordance with the alert service bulletin.

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Seattle Aircraft Certification Office (ACO), FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Seattle ACO.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Seattle ACO.

(c) Special flight permits may be issued in accordance with §§ 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Issued in Renton, Washington, on October 7, 1998.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98-27481 Filed 10-13-98; 8:45 am]
BILLING CODE 4910-13-U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 315 and 601

[Docket No. 98N-0040]

Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring; Extension of Comment Period

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; extension of comment period.

SUMMARY: The Food and Drug Administration (FDA) is extending to November 16, 1998, the comment period on a proposed rule that was published in the *Federal Register* of May 22, 1998 (63 FR 28301). The document proposed to amend the drug and biologics regulations by adding

provisions that would clarify the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring. The agency is taking this action to provide interested persons additional time to submit comments to FDA on the proposed rule.

DATES: Written comments by November 16, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Dano B. Murphy, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210, or Brian L. Pendleton, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5649.

SUPPLEMENTARY INFORMATION: In the *Federal Register* of May 22, 1998 (63 FR 28301), FDA published a proposed rule to amend the drug and biologics regulations by adding provisions that would clarify the evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis and monitoring of diseases. The proposed regulations would describe certain types of indications for which FDA may approve diagnostic radiopharmaceuticals. The proposed rule would also include criteria that the agency would use to evaluate the safety and effectiveness of a diagnostic radiopharmaceutical under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. FDA provided until August 5, 1998, to submit comments on the proposed rule.

In the *Federal Register* of August 3, 1998 (63 FR 41219), FDA extended the comment period on the proposed rule until October 15, 1998, to allow interested persons additional time to submit comments on the proposed rule. FDA finds it appropriate to further extend the comment period to November 16, 1998, to permit interested persons the opportunity to consider the proposed rule in light of the agency's draft guidance for industry entitled "Developing Medical Imaging Drugs and Biologics." Notice of the availability of this draft guidance is published elsewhere in this issue of the *Federal Register*.

Interested persons may, on or before November 16, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposed rule. Two copies of any

comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98-27494 Filed 10-13-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 315 and 601

[Docket No. 98D-0785]

Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Availability of guidance.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Developing Medical Imaging Drugs and Biologics." This draft guidance is intended to assist developers of drug and biological products used for medical imaging, as well as radiopharmaceutical drugs used in disease diagnosis, in planning and coordinating the clinical investigations of, and submitting various types of applications for, such products. The draft guidance also provides information on how the agency will interpret and apply provisions in the proposed regulations for in vivo radiopharmaceuticals used for diagnosis and monitoring, which published in the *Federal Register* of May 22, 1998 (63 FR 28301).

DATES: Written comments on the draft guidance may be submitted by December 14, 1998. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), 1401

Rockville Pike, Rockville, MD 20852-1448, FAX 888-CBERFAX or 301-827-3844. Send two self-addressed adhesive labels to assist the office in processing your request. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Requests and comments should be identified with the docket number found in brackets in the heading of this document. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT:

Robert K. Leedham, Jr., Center for Drug Evaluation and Research (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 30857, 301-443-3500, or George Q. Mills, Center for Biologics Evaluation and Research (HFM-573), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-5097.

SUPPLEMENTARY INFORMATION:

I. Description of the Guidance

FDA is announcing the availability of a draft guidance document entitled "Developing Medical Imaging Drugs and Biologics." It references other CDER and CBER guidance documents that relate to the development of medical imaging drugs and biologics, including CBER's "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (62 FR 9196, February 28, 1997). The draft guidance is intended to assist developers of drug and biological products used for medical imaging, as well as radiopharmaceutical drugs used in disease diagnosis, in planning and coordinating the clinical investigations of, and submitting various types of applications for, such products. The draft guidance applies to medical imaging drugs that are used for diagnosis and monitoring and that are administered in vivo. Such drugs include contrast agents used with medical imaging techniques such as radiography, computed tomography, ultrasonography, and magnetic resonance imaging, as well as radiopharmaceuticals used with imaging procedures, such as single-photon emission computed tomography and positron emission tomography. The draft guidance is not intended to apply to possible therapeutic uses of these drugs or to in vitro diagnostic products.

CDER's Division of Medical Imaging and Radiopharmaceutical Drug Products presented a preliminary version of this draft guidance document to the Medical

Imaging Drug Advisory Committee (MIDAC) on October 26, 1996.

Following that meeting, FDA worked with MIDAC to develop this draft guidance. As part of this process, FDA considered proposals submitted by an ad hoc group representing contrast agent manufacturers and by the Council on Radionuclides and Radiopharmaceuticals, Inc.

On November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

Section 122(a)(1) of the Modernization Act directs FDA to issue regulations on the approval of diagnostic radiopharmaceuticals. In the **Federal Register** of May 22, 1998 (63 FR 28301), FDA published a proposed rule on the evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis and monitoring of diseases. The proposed rule describes certain types of indications for which FDA would approve diagnostic radiopharmaceuticals and lists factors that the agency would consider in evaluating the safety and effectiveness of a diagnostic radiopharmaceutical under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act). This draft guidance document provides information on how FDA intends to interpret and apply various sections of the proposed rule.

In the **Federal Register** of August 3, 1998 (63 FR 41219), FDA published a document extending the comment period on the proposed rule on in vivo radiopharmaceuticals from August 5, 1998, to October 15, 1998. In a separate document published elsewhere in this issue of the **Federal Register**, FDA is further extending the comment period to November 16, 1998. FDA hopes that the issuance of this draft guidance on medical imaging drugs and biologics, in conjunction with the extension of the comment period on the proposed rule, will assist interested persons in preparing their comments on the proposed rule. Persons will have additional time to submit comments on the draft guidance after the comment period on the proposed rule closes.

This draft level 1 guidance is being issued consistent with FDA's good guidance practices (62 FR 8961, February 27, 1997). It represents the agency's current thinking on the development of medical imaging drugs and biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the

requirements of the applicable statutes, regulations, or both.

II. Comments

Interested persons may, at any time, submit to the Dockets Management Branch (address above) written comments on the draft guidance document. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document. The draft guidance document and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

III. The Paperwork Reduction Act of 1995

This draft guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). A description of these provisions is provided in the following paragraphs with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comment on the following: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics

Description: FDA is issuing a draft guidance on the development of medical imaging drugs and biologics. The draft guidance is intended to assist developers of drug and biological products used for medical imaging, as well as radiopharmaceutical drugs used in disease diagnosis, in planning and coordinating the clinical investigations of, and submitting various types of applications for, such products. The draft guidance provides information on

how the agency will interpret and apply provisions of the existing regulations regarding the content and format of an application for approval of a new drug (21 CFR 314.50) and the content of a biological product application (21 CFR 601.25). In addition, the draft guidance provides information on how the agency will interpret and apply the proposed rule on the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring (63 FR 28301). The proposed rule, by adding part 315, would clarify existing FDA requirements for the evaluation and approval of drug and biological radiopharmaceuticals already in place under the authority of the act and the PHS Act.

Existing regulations, which appear primarily in parts 314 and 601 (21 CFR parts 314 and 601), specify the information that manufacturers must submit so that FDA may properly evaluate the safety and effectiveness of new drugs and biological products. This information is usually submitted as part of a new drug application (NDA) or a biologics license application (BLA), or as a supplement to an approved application. This draft guidance supplements these regulations. Under the proposed rule and the draft guidance, information required under the act and the PHS Act and needed by

FDA to evaluate safety and effectiveness would still have to be reported.

Description of Respondents: Manufacturers of medical imaging drugs and biologics, including contrast drug products and diagnostic radiopharmaceuticals.

Burden Estimate: The proposed rule on in vivo radiopharmaceuticals used for diagnosis and monitoring sets forth an estimated annual reporting burden on the industry that would result from that rulemaking (63 FR 28301 at 28305 to 28306). This draft guidance on the development of medical imaging drugs and biologics is in part intended to explain how FDA will interpret and apply the proposed rule. Thus, the estimated annual reporting burden of the draft guidance, as provided in the chart below, is the same as that of the proposed rule, with one change. In addition to the diagnostic radiopharmaceuticals that are the subject of the proposed rule, the draft guidance also addresses the development of contrast drug products, which FDA evaluates and approves under part 314, but which are not affected by the proposed rule.

The chart below provides an estimate of the annual reporting burden for diagnostic radiopharmaceuticals and is based on the estimate described in the proposed rule (63 FR 28301 at 28306). The chart also provides an estimate for

the annual reporting burden for contrast drug products. FDA estimates that the potential number of respondents who would submit applications or supplements for contrast drug products would be one. Although FDA did not approve any NDA's for contrast drugs (there are no biological contrast drug products) in fiscal year 1997 (FY 1997), for purposes of estimating the annual reporting burden, the agency assumes that it will approve one contrast drug each fiscal year. The annual frequency of responses for contrast drugs is estimated to be one response per application or supplement. The hours per response, which is the estimated number of hours that an applicant would spend preparing the information to be submitted for a contrast drug in accordance with this draft guidance, is estimated to be approximately 2,000 hours.

The draft guidance would not impose any additional reporting burden because safety and effectiveness information is already required by existing regulations. In fact, clarification by the draft guidance of FDA's standards for evaluation of medical imaging drugs and biologics is expected to reduce the overall burden of information collection. FDA invites comments on this analysis of information collection burdens.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours	
Diagnostic Radiopharmaceuticals	8	1	8	2,000	16,000
Contrast Drugs	1	1	1	2,000	2,000
Total					18,000

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with section 3507(d) of the PRA (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this draft guidance to OMB for review. Interested persons are requested to send comments on this information collection by November 13, 1998, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

IV. Electronic Access

An electronic version of this draft guidance document is available on the Internet using the World Wide Web (WWW) at "<http://www.fda.gov/cder/guidance/index.htm>" or "<http://www.fda.gov/cber/guidelines.htm>".

Dated: October 6, 1998.

William K. Hubbard,
Associate Commissioner for Policy
Coordination.

[FR Doc. 98-27495 Filed 10-13-98; 8:45 am]

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DEPARTMENT OF JUSTICE

Office of Juvenile Justice and Delinquency Prevention

28 CFR Part 31

[OJP (OJJDP)-1158]

RIN 1121-AA46

Juvenile Accountability Incentive Block Grants

AGENCY: Office of Juvenile Justice and Delinquency Prevention (OJJDP), Office of Justice Programs, Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: This document proposes procedures under which an eligible State, or unit of local government that receives a subgrant from the State, is

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY¹

Developing Medical Imaging Drugs and Biologics

I. INTRODUCTION

This guidance is intended to assist developers of medical imaging drug and biological products in planning and coordinating their clinical investigations and preparing and submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated NDAs (ANDAs), and supplements to NDAs or BLAs.

Medical imaging drugs are generally governed by the same regulations as other drug and biological products.² However, as described in this document, many medical imaging drugs have special characteristics that can help guide developmental efforts. This guidance discusses some of these special characteristics and how drug development for medical imaging drugs can be tailored to reflect those characteristics. Specifically, this guidance discusses the following items:

1. Potential claims for medical imaging drugs and the nature of promotional materials for such claims.³
2. Methods by which each of these claims may be established.
3. Special considerations in the clinical evaluation of efficacy.
4. Special considerations in the clinical evaluation of safety.

¹ This guidance has been prepared by the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER) and the Office of Therapeutics Research and Review in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on developing medical imaging drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

² Sponsors developing medical imaging drugs should be familiar with Agency regulations and guidances pertaining to the development of drugs and biologics.

³ The terms *claim*, *indication*, and *indication for use* are used interchangeably in this guidance.

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In response to the requirements of the FDA Modernization Act of 1997, FDA recently proposed a rule to amend the drug and biologics regulations for one category of medical imaging drugs by adding provisions for the evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis or monitoring of diseases (63 FR 28301, May 22, 1998). This guidance elaborates on the concepts contained in the proposed rule on radiopharmaceutical diagnostic products. Once the proposal is finalized, the Agency will revise this guidance, if necessary, to ensure that it is consistent with the final rule.

II. SCOPE: TYPES OF MEDICAL IMAGING DRUGS

This guidance applies to medical imaging drugs that are used for diagnosis or monitoring and that are administered in vivo. These include medical imaging drugs used with medical imaging techniques such as radiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and radionuclide imaging. The guidance is not intended to apply to the development of therapeutic uses or to in vitro diagnostic uses of these drugs.

Medical imaging drugs can be classified into two general categories:

A. Contrast Drug Products

Contrast drug products are used to increase the relative difference of signal intensities in adjacent parts of the body and to provide additional information in combination with an imaging device beyond that obtained by the device alone. These products include, but are not limited to, the following: (1) iodinated compounds used in radiography and CT; (2) paramagnetic metallic ions (such as ions of gadolinium, iron, and manganese) linked to a variety of molecules and used in MRI; and (3) microbubbles, microaerosomes, and related microparticles used in diagnostic ultrasonography.

B. Diagnostic Radiopharmaceuticals⁴

⁴ As defined in the proposed rule for diagnostic radiopharmaceuticals, and as used in this guidance, a *diagnostic radiopharmaceutical* is (a) an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons or (b) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such an article. The FDA interprets this definition to include articles that exhibit spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons (63 FR 28301 at 28303).

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Diagnostic radiopharmaceuticals are radioactive drugs that contain a radioactive nuclide that may be linked to a ligand or carrier.⁵ These products are used in planar imaging, single photon emission computed tomography (SPECT), positron emission tomography (PET), or with other radiation detection probes.

Diagnostic radiopharmaceuticals used for imaging typically have two distinct components:

1. A radionuclide that can be detected *in vivo* (e.g., technetium-99m, iodine-123, indium-111). The radionuclide typically is a radioactive molecule with a relatively short physical half-life that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. These photons may then be detected with imaging devices or other detectors.
2. A nonradioactive component that delivers the molecule to specific areas within the body. This nonradionuclidic portion of the diagnostic radiopharmaceutical often is an organic molecule such as a carbohydrate, lipid, nucleic acid, peptide, small protein, or antibody. In general, the purpose of the nonradioactive component is to direct the radionuclide to a specific body location or process.

III. INDICATIONS FOR MEDICAL IMAGING DRUGS

Because medical imaging drugs are used clinically in many diverse ways, this guidance outlines certain types of potential claims for these drugs. For example, some medical imaging drugs are not intended to provide disease-specific information, as characterized by measures such as sensitivity and specificity, but are intended to characterize structural or functional manifestations common to several diseases. In such cases, the proposed indications for these products may refer to structural or functional assessments that are common to multiple diseases or conditions.

Indications for medical imaging drugs may fall within the following general categories:

- Structure delineation
- Functional, physiological, or biochemical assessment
- Disease or pathology detection or assessment
- Diagnostic or therapeutic patient management

⁵ In this guidance, the terms *ligand* and *carrier* refer to the entire nonradionuclidic portion of the diagnostic radiopharmaceutical.

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These claims need not be mutually exclusive, and approval may be possible for claims other than those listed. Each of these claims is described in the following sections as is the nature of promotional materials for each of these claims. Ways in which each of these claims may be established are described in Section IV.

A. Structure Delineation

As described in the following sections, two types of claims for structure delineation may be possible: (1) locating and outlining normal anatomic structures and (2) distinguishing between normal and abnormal anatomy.

1. Locating and Outlining Normal Anatomic Structures

A medical imaging drug approved for this type of claim should be able to help locate and outline normal anatomic structures. The product also should help clarify the spatial relationship of the visualized normal structure(s) with respect to other body parts or structures.

Such a medical imaging drug may be developed to distinguish a normal structure that may not be seen well with other imaging drugs or modalities. For example, a contrast drug product may be developed to delineate the normal gastrointestinal tract to distinguish it from other abdominal structures or an abdominal mass. Similarly, a diagnostic radiopharmaceutical may be developed to image the normal parathyroid glands, which could help a surgeon plan and perform surgery for a mass in the thyroid gland. Products that help delineate normal anatomic variants also may be included here. An example of this type of product is a drug that delineates normal variants of coronary anatomy.

Promotional materials based on this claim may describe how the medical imaging drug enhances visualization of the normal anatomic structure, or its variants, and how it facilitates an understanding of the relationship of the normal visualized structure to other structures. However, promotional materials based on these claims should not imply that use of the product helps distinguish normal and abnormal anatomy, or that the product aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients. These types of uses fall within other claims.

2. Distinguishing Between Normal and Abnormal Anatomy

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A medical imaging drug approved for this type of claim should be able to help locate and outline both normal and abnormal anatomic structures. The product also should help to clarify the spatial relationships of the normal and abnormal anatomic structure(s) with respect to other body parts or structures. This type of claim applies to situations where the mechanism by which the abnormal anatomy is visualized is sufficiently similar to the mechanism by which the normal anatomy is visualized. This type of claim does not apply to products whose mechanism of visualization is dependent on the presence of an abnormality.

Examples of this type of product include a medical imaging drug being developed to identify bronchiectasis. The drug might be able to distinguish dilated bronchi from normal bronchi and categorize the bronchiectasis anatomically (e.g., as cylindrical, sacculated, or fusiform). Similarly, a medical imaging drug might be developed to evaluate meniscal or ligamentous injuries of the knee. Products that help delineate anomalous variants of normal anatomy may also be included here (e.g., a product that helps define the anatomical relationships of a vascular sling that compresses the trachea or esophagus).

Promotional materials based on such a claim may describe how the medical imaging drug helps distinguish between normal and abnormal anatomy or aids in identification of variants or anomalies of normal anatomy. Promotional materials based on these claims should not imply, beyond the description of the abnormal anatomy, that the product aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients.

A medical imaging drug that is intended either to (a) delineate nonanatomic structures such as tumors or abscesses or (b) detect disease or pathology within an anatomic structure should seek a claim of *disease or pathology detection or assessment or diagnostic or therapeutic patient management*, rather than this claim.

B. Functional, Physiological, or Biochemical Assessment

A medical imaging drug that is intended to provide functional, physiological, or biochemical assessment should be able to evaluate the function, physiology, or biochemistry of a tissue, organ system, or body region. Functional, physiological, and biochemical assessments are designed to determine if a measured parameter is normal or abnormal. This type of claim applies to drugs used to detect either a reduction or magnification of a normal functional, physiological, or biochemical process.

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Examples of functional, physiological, or biochemical assessments include measurement of cardiac ejection fraction, assessment of regional cerebral blood flow, evaluation of myocardial wall motion, and assessment of anaerobic metabolites to evaluate tissue ischemia.

Promotional materials based on this type of claim may describe how the medical imaging drug facilitates assessments of function, physiology, or biochemistry. Promotional materials based on these claims should not imply that the use of these products aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients.

The claim of *functional, physiological, or biochemical assessment* is limited to assessment of normal functional, physiological, or biochemical processes when disturbances of these processes are common to several diseases or conditions and they are not diagnostic for any particular disease or condition. When these circumstances are not present, claims of *disease or pathology detection or assessment or diagnostic or therapeutic patient management* should be sought. For example, a claim of *disease or pathology detection or assessment* should be sought by sponsors who wish to develop a medical imaging drug to:

- Establish a diagnosis by detecting or assessing the function, physiology, or biochemistry of a tissue, organ system, or body region;
- Detect or assess an abnormality of function, physiology, or biochemistry that is diagnostic for a disease or condition;
- Detect or assess an abnormality of function, physiology, or biochemistry that is diagnostic for a specific disease or condition in the defined clinical setting for which the test will be indicated and used (see Section III.C);
- Detect or assess functional, physiological, or biochemical processes that are not expressed by the normal organ system, tissue, or body part.

C. Disease or Pathology Detection or Assessment

A medical imaging drug that is intended for disease or pathology detection or assessment should be able to assist in the detection, location, or characterization of a specific disease or pathological state in a defined clinical setting.⁶

⁶ See Section IV.C for a definition of *defined clinical setting*.

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Examples of medical imaging drugs for this type of indication include (1) a peptide that participates in an identifiable transporter function associated with a specific neurological disease; (2) a peptide that is specifically metabolized and is used to evaluate an abnormal cell's residual metabolic function in a particular disorder; and (3) a radiolabeled monoclonal antibody that attaches to a tumor antigen and thus detects a tumor.

Promotional materials based on this claim may describe how the medical imaging drug facilitates detection or assessment of a specific disease or pathology in the defined clinical setting in which it was studied. Promotional materials based on this claim should not imply that use of these products leads to particular changes in diagnostic or therapeutic patient management or in clinical outcomes.

D. Diagnostic or Therapeutic Patient Management

A medical imaging drug that is intended to assist in diagnostic or therapeutic patient management may be studied explicitly for its ability to provide imaging or related information leading directly to appropriate diagnostic or therapeutic management decisions in patients in a defined clinical setting. In this context, *explicitly* means that the hypotheses of how the medical imaging drug might be useful in diagnostic or therapeutic management should be specified in the protocol. Hypotheses should be tested prospectively in the clinical study and should be evaluated with endpoints that assess the appropriateness of patient management or clinical outcomes.⁷ For example, a medical imaging drug may assist in appropriate determination of whether patients (1) should undergo diagnostic coronary angiography (i.e., the test results aid in a diagnostic management decision); (2) will have predictable clinical benefit from coronary revascularization (i.e., the test results aid in a therapeutic management decision); or (3) should undergo resection of a tumor or undergo chemotherapy (i.e., the test results aid in therapeutic management decisions). Labeling indications for these examples might include statements that a drug is indicated *to help determine the need for coronary angiography or to assist in the evaluation of tumor resectability*.

Promotional materials for this type of claim may describe how the medical imaging drug assists in diagnostic or therapeutic patient management.

E. Multiple Claims

The indication categories outlined above are flexible, and claims for medical imaging drugs need not be mutually exclusive. For example, a diagnostic radiopharmaceutical may be

⁷ As used in this guidance, *clinical outcomes* refers to changes in patient symptoms, functioning, or survival.

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developed as an aid in the diagnosis of lung cancer for a claim of *disease or pathology detection or assessment*. This diagnostic radiopharmaceutical could also be evaluated for its ability to provide information that leads directly to appropriate therapeutic management decisions (e.g., helping to determine, based on test results, what combination of surgery, radiotherapy, and chemotherapy might be appropriate).

Clinical studies should usually evaluate the effect of the imaging agent on both structure and function when both are commonly evaluated together in clinical practice (e.g., as during ultrasonography). For example, an ultrasound contrast drug used to assess stenotic blood vessels could be approved for both structural delineation and functional assessment if appropriate clinical studies were performed. In this case, clinical studies could be designed so that structural delineation of blood vessels is evaluated with two-dimensional ultrasonographic imaging. The functional assessment of the hemodynamic consequences of the obstructions could be evaluated with Doppler interrogation of the same vessels.

F. Other Claims

For a claim that does not fall within the indication categories identified above, the applicant or sponsor should consult FDA on the nature of the desired claim and how to establish effectiveness for it.

IV. ESTABLISHING CLAIMS FOR MEDICAL IMAGING AGENTS

To establish a claim for a medical imaging drug, a sponsor or applicant should characterize the drug's clinical usefulness and demonstrate that the information provided is valid and reliable.⁸ Clinical studies should be performed in defined clinical settings. These overarching principles are discussed in this section, as are the methods of establishing effectiveness for specific claims.

A. Clinical Usefulness

The principal reason for performing an evaluation with a medical imaging drug is to determine that the diagnostic results will be useful to the patient and the health care provider. As is the case with therapeutic drugs, claims for medical imaging drugs should be supported with information demonstrating that the potential benefits of the use of a medical imaging drug outweigh the potential risks to the patient. Potential risks include

⁸ As used in this guidance, *validity* is a global concept that encompasses the quality of bias. Valid measurements are close to the *truth* (have small bias). *Reliability* is a concept that encompasses the quality of precision. Reliable measurements are reproducible (have small variance).

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both the risks related to administration of the drug and the risks of incorrect diagnostic information. Incorrect diagnostic information includes, but is not limited to, inaccurate structural, functional, physiological, or biochemical information; false positive or false negative diagnostic determinations; and information leading to inappropriate decisions in diagnostic or therapeutic management.

A medical imaging drug that is clinically useful provides information that contributes to the appropriateness of diagnostic or therapeutic patient management, contributes to beneficial clinical outcome, or provides accurate prognostic information.

In addition, for a contrast drug product to be considered clinically useful, the product used in combination with an imaging device should provide useful information beyond that obtained by the imaging device alone. Stated differently, imaging with the contrast drug product should add value when compared to imaging without the contrast drug product.

A plan for establishing clinical usefulness should be incorporated into the development plan of a medical imaging drug. In general, clinical usefulness should be evaluated prospectively in the principal clinical studies of efficacy (e.g., by incorporation into Phase 3 protocols).⁹

B. Validity of Information Provided by a Medical Imaging Drug

A medical imaging drug may be shown to provide valid information in at least two ways:

1. Comparing the results yielded by the medical imaging drug with those of a truth standard (*gold standard*).¹⁰
2. Demonstrating that the use of the product contributes to beneficial patient outcomes.

In instances where a truth standard does not exist or cannot be assessed practically, the focus of the study should be to evaluate the effects of the product on clinical outcomes. For example, clinical outcomes could be assessed in a study designed to evaluate the effects of the medical imaging drug on *diagnostic or therapeutic management* (see Section IV.D.4).

⁹ In some situations (e.g., measurement of cardiac ejection fraction), clinical usefulness may be documented by a critical and thorough analysis of the medical literature and any historical precedents.

¹⁰ See Glossary and Section VIII.C.

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C. Defined Clinical Settings

A *defined clinical setting* should reflect the circumstances and conditions under which the medical imaging drug is intended to be used. It delineates the patient population, relevant available medical and diagnostic data, and diagnostic questions that characterize the circumstances under which the medical imaging drug is intended to be used. For example, a medical imaging drug for duodenal ulcers could be developed for use in different defined clinical settings. The drug might be developed to identify or exclude duodenal ulcers in patients with gastrointestinal bleeding, to confirm a suspected duodenal ulcer in patients with equivocal findings on radiographic examination of the upper gastrointestinal tract, to evaluate healing of duodenal ulcers in patients after initial treatment, or to help determine whether patients with duodenal ulcers should undergo surgery or remain on maintenance medical therapy.

The circumstances and conditions under which the medical imaging drug is intended to be used should be evaluated in a clinical trial and may be described in the labeling using the following mechanisms.

1. Specifying aspects of the medical history and physical examination that are pertinent for determining the likelihood of the disease or condition that is in question. For example, a medical imaging drug intended to detect breast cancer might be evaluated for use in the assessment of (1) otherwise healthy women over 40 years of age, (2) women presenting with palpable breast masses, or (3) women with a family history of breast cancer.
2. Specifying a patient population that is at a particular step in the diagnostic sequence. For example, a diagnostic radiopharmaceutical may be intended to evaluate patients in an emergency room with equivocal clinical and laboratory findings of a myocardial infarction, or to evaluate the location and extent of a myocardial infarction in patients with definitive findings.
3. Specifying any other diagnostic assessments that are to be performed in the evaluation of this patient population. This delineation should include describing how the medical imaging drug should be used with respect to other diagnostic tests or evaluations, including (1) whether the medical imaging drug is intended to be used together with, or as a replacement for, other diagnostic tests or modalities, and (2) how the use of the medical imaging drug is influenced by the results of other diagnostic evaluations. For example, in the evaluation of suspected pulmonary embolism, a medical imaging drug could be developed either as a replacement for ventilation-

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perfusion scanning or as an adjunct to ventilation-perfusion scanning. If the medical imaging drug is developed to be an adjunct to ventilation-perfusion scanning, its intended use will likely be influenced by the scan results (e.g., intended for use in patients with scan results that are indeterminate and not for patients with *low-probability* or *high-probability* scans).

Clinical trials should prospectively evaluate relevant hypotheses about the demarcated patient population in the clinical setting in which the drug is intended to be used.

D. Establishing Effectiveness for Specific Claims

The following sections describe how each of the types of claims summarized in Section III may be established.

1. Structure Delineation

Methods by which claims for *structure delineation* may be established are described below.

a. Locating and Outlining Normal Anatomic Structures

A claim of *delineating normal anatomic structures* may be established by demonstrating in clinical studies that the medical imaging drug can reliably locate and outline normal anatomic structures and reliably clarify the spatial relationship of these structures to other body parts.

In clinical studies, the validity of the delineation should be demonstrated by comparing the performance of the medical imaging drug with that of a reference product or procedure of known high validity (i.e., a truth standard). Ideally, the high validity of this reference product or procedure should be thoroughly and critically documented before initiating the clinical efficacy studies.

In some cases, valid reference products or procedures may not be available or cannot be used. In these cases, the validity of the medical imaging drug may be demonstrated with clinical studies documenting that the product provides information that is consistent with known anatomic and structural facts about the tissue, organ, or body part in question. The sponsor should

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discuss these anatomic and structural facts with the Agency and carefully detail and document them prior to initiation of the clinical efficacy studies.

b. Distinguishing Between Normal and Abnormal Anatomy

A claim for *distinguishing between normal and abnormal anatomy* may be established by demonstrating in clinical studies that the medical imaging drug can reliably locate and outline both normal and abnormal variations of an anatomic structure, and that the product is able to clarify the spatial relationships of the normal and abnormal anatomic structures with respect to other body parts or structures.

The validity of this distinction should be supported by studies in which sufficient numbers of subjects with and without abnormalities are appropriately represented. *Appropriate representation* means that the studies should generally include subjects that adequately represent the spectra of normality and abnormality (e.g., including subjects with chronic bronchitis, pneumonia, asthma, and cystic fibrosis; and also subjects with localized and diffuse disease for a drug intended to assess bronchiectasis) as well as the full range of disease severity (e.g., from mild to severe disease, or from early to advanced disease).

Appropriate preclinical studies in relevant animal models, if available, may provide additional information to support structure-delineation claims.

2. Functional, Physiological, or Biochemical Assessment

This type of claim may be established by demonstrating in clinical studies that the medical imaging drug can reliably measure a function or a physiological or biochemical process. These measurements should generally be validated by comparing the performance of the medical imaging drug with that of a reference product or procedure of known high validity (i.e., a truth standard). Ideally, the high validity of this reference product or procedure should be thoroughly and critically documented before its use in clinical studies.

These studies should provide a quantitative or qualitative understanding of how the measurement varies in normal and abnormal subjects or tissues, including the parameter's normal range, distribution, and confidence intervals in these subjects or tissues. When possible, the minimum detectable limits and reproducibility of the measurement should be assessed.

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The parameter should be evaluated in sufficient numbers of both normal and abnormal patients. These patients should adequately represent the full spectra of normality and abnormality (e.g., including patients with inflammatory, neoplastic, and infectious intracranial processes for a drug intended to assess regional cerebral blood flow) and the full range of functional, physiological, or biochemical dysfunction (e.g., from minimal or no perfusion to luxury perfusion).

The drug's pharmacology in the setting of various functional, physiologic, or biochemical processes also should be documented from appropriate studies in relevant animal species, if available. These might include approaches such as induction of pharmacologic perturbations in the system to be evaluated (e.g., administration of a specific receptor antagonist that results in altered binding of the medical imaging drug); correlation with other accepted means of measuring particular parameters (e.g., evaluation of the cardiac ejection fraction by comparison to results obtained with radionuclide ventriculography); and in vivo or in vitro analyses (e.g., tissue autoradiography). Documentation should be obtained in at least one appropriate and relevant animal species, if available, in which the particular function, physiology, or biochemistry is sufficiently similar to that of humans. For example, for a medical imaging drug being developed to evaluate receptors within the central nervous system, full biochemical characterization of rodent brains by tissue autoradiography may be appropriate.

3. Disease or Pathology Detection or Assessment

A claim of *disease or pathology detection or assessment* may be established by demonstrating in a defined clinical setting that the medical imaging drug is able to identify or characterize the disease or pathology with sufficient validity and reliability. In this context, the term *validity* refers to the overall diagnostic performance of the product as measured by factors such as sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios. *Reliability* in this context means that the overall diagnostic performance of the product has precision. The phrase *sufficient validity and reliability* means validity and reliability that are good enough to indicate that the product could be useful in one or more defined clinical settings.

Data demonstrating validity and reliability should be obtained from patients in defined clinical settings reflecting the proposed indications. Patients may present for diagnostic evaluation of a specific disease or condition in various clinical settings. Even though these patients may have the same disease or condition, the clinical usefulness of the medical imaging drug and the likelihood that patients have

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the disease or condition will likely be different in each clinical setting. Therefore, the medical imaging drug should be evaluated in representative settings for which use is proposed. In most disease or pathology detection or assessment indications, pooling of efficacy data across defined clinical settings would likely be of limited value, and the medical imaging drug should be separately evaluated in sufficient numbers of patients in one or more of such settings. A claim for disease or pathology detection or assessment may specify the defined clinical setting and specify that the medical imaging drug is to be used in conjunction with other tests.

4. Diagnostic or Therapeutic Patient Management

A claim of *diagnostic or therapeutic patient management* may be established in clinical studies by demonstrating that in a defined clinical setting the test is useful in guiding appropriate patient management. *Appropriate patient management* means that diagnostic or therapeutic management decisions are validated as being proper based on the correct diagnosis of the patient or on clinical outcomes. The correct diagnosis may be documented by comparison with valid assessments of actual clinical status (e.g., a histological diagnosis of malignancy), through patient follow-up, or by evaluation of clinical outcomes.

Medical imaging drugs may seek the claims *disease or pathology detection or assessment*, or *diagnostic or therapeutic management*, or both. A clarification of the distinction between these claims is appropriate. The claim *disease or pathology detection or assessment* can be obtained by demonstrating, in a defined clinical setting, sufficient validity and reliability of the medical imaging drug to imply clinical usefulness. The claim *diagnostic or therapeutic management* will likely be more difficult to establish, given the same defined clinical setting. Generally, it will require prospectively designed trials with the objective of evaluating a specific hypothesis of how the medical imaging drug might be useful in diagnostic or therapeutic patient management in a defined clinical setting. The trials might include randomization (whether to receive the medical imaging drug), with an endpoint measuring appropriateness of management (given the ultimate correct diagnosis) or clinical outcome. Alternatively, all patients may receive the study drug if it is possible to determine both what the management would have been had the medical imaging drug not been used, and what the management would be because of information provided by the medical imaging drug. The trials should demonstrate that management based on findings using the medical imaging drug is superior to management without use of the medical imaging drug. A *patient management* claim may specify that the medical imaging drug is to be used in conjunction with other tests to affect a patient management decision.

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V. GENERAL CONSIDERATIONS FOR SAFETY ASSESSMENTS OF MEDICAL IMAGING DRUGS

The safety evaluation of a medical imaging agent is generally similar to those of other drugs and biologics. However, in many cases, the special characteristics of medical imaging drugs allow nonclinical and clinical safety assessments to be relatively efficient. The following sections discuss the special characteristics of a medical imaging drug that may lead to a more focused safety evaluation. These characteristics include its dose or mass, route of administration, frequency of use, and biological, physical, and effective half-lives.¹¹

A. Dose or Mass

Medical imaging drugs may be administered at low mass doses. For example, the mass of a single dose of a diagnostic radiopharmaceutical may be relatively small because device technologies can typically detect small amounts of a radionuclide. When a medical imaging drug is administered at a mass dose that is at the low end of the dose-response curve for adverse events, dose-related adverse events are less likely to occur.

B. Route of Administration

Some medical imaging drugs are administered by routes that decrease the likelihood of systemic adverse events. For example, medical imaging drugs that are administered as contrast media for radiographic examination of the gastrointestinal tract (e.g., barium sulfate) may be administered orally, through an oral tube, or rectally. In patients with normal gastrointestinal tracts, many of these products are not absorbed. Accordingly, systemic adverse events are less likely to occur in these patients. Therefore, after a sponsor demonstrates that such a product is not absorbed systemically in the population proposed for use, the product may be able to undergo a more efficient safety evaluation that primarily assesses local organ system toxicity, toxicities that are predictable (e.g., volume effects, aspiration), and effects after intraperitoneal exposure (e.g., after gastrointestinal perforation). However, if the product will be used in patients with gastrointestinal pathologies that increase absorption, more complete nonclinical and clinical safety evaluations should be performed.

¹¹ See also the proposed rule on developing diagnostic radiopharmaceuticals (63 FR 28301, May 22, 1998). When a medical imaging drug does not possess any special characteristics, complete standard drug safety assessments should be performed.

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C. Frequency of Use

Many medical imaging drugs, including both contrast drug products and diagnostic radiopharmaceuticals, are administered relatively infrequently and in single doses. Accordingly, adverse events that are related to long-term use or to drug accumulation are less likely to occur with these drugs than with drugs that are administered chronically. Therefore, the nonclinical and clinical development programs for such products may generally omit long-term, or traditional, repeat-dose safety studies. However, in clinical settings where it is likely that the medical imaging drug will be administered repeatedly (e.g., to monitor disease progression), repeat-dose studies should be performed to assess safety and efficacy.

D. Biological, Physical, and Effective Half-Lives¹²

Diagnostic radiopharmaceuticals may use radionuclides with short physical half-lives or may be excreted rapidly. The biological, physical, and effective half-lives of diagnostic radiopharmaceuticals are incorporated into radiation dosimetry evaluations that require an understanding of the kinetics of the distribution and excretion of the radionuclide and its mode of decay. Biological, physical and effective half lives should be taken into account in planning appropriate safety and dosimetry evaluations of diagnostic radiopharmaceuticals (see Sections VI. and XI.C).

VI. NONCLINICAL SAFETY ASSESSMENTS

The special characteristics of medical imaging drugs described above may allow for a more efficient nonclinical safety program. The nonclinical development strategy for a drug should be based on sound scientific principles; the drug's unique chemistry (including, for example, those of its components, metabolites, and impurities); and the drug's intended use. Sponsors are encouraged to consult with the Agency before submission of an IND application and during drug development for recommendations and advice about the overall nonclinical development plan and proposed nonclinical protocols. In part, the number and types of nonclinical studies that should

¹² *Biological half-life* is the time needed for a human or animal to remove, by biological elimination, half of the amount of a substance that has been administered. *Effective half-life* is the time needed for a radionuclide in a human or animal to decrease its activity by half as a combined result of biological elimination and radioactive decay. *Physical half-life* is the time needed for half of the population of atoms of a particular radioactive substance to disintegrate to another nuclear form.

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be conducted depend on the phase of the drug's development, what is known about the drug or its drug class, its proposed use, and the indicated patient population.

In the discussion that follows, a distinction is made between biological products and drug products. Existing specific guidance for biological products is referenced but not repeated here.

A. Nonclinical Safety Assessments for Biological Products

Many biological products raise relatively distinct nonclinical issues (e.g., immunogenicity and species restrictions). To ensure consistency with section 351 of the Public Health Service Act, the following documents should be reviewed for guidance on the preclinical evaluation of biological medical imaging agents:

- *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, ICH, November 1997.
- *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, February 27, 1997.

B. Nonclinical Safety Assessments for Non-Biological Products

The following sections describe ways in which nonclinical assessments of safety may be performed for non-biological contrast drug products and diagnostic radiopharmaceuticals.

1. Contrast drug products

Because of the characteristics of contrast drug products and the way they are used, nonclinical safety evaluations of such drug products may be made more efficient with the following modifications:

- Long-term, repeat-dose toxicity studies in animals usually can be eliminated.
- Long-term rodent carcinogenicity studies usually can be omitted.¹³
- Reproductive toxicology studies can often be limited to an evaluation of embryonic and fetal toxicities in rats and rabbits and to evaluations of

¹³ Circumstances in which carcinogenicity testing may be recommended are summarized in the ICH guidance S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals, March 1, 1996.

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reproductive organs in other short-term toxicity studies.¹⁴ However, a justification should be provided for any studies of reproductive toxicology that are not performed and a formal request should be made to waive them.¹⁵

Additional safety considerations for contrast drug products may include the following: their large mass dose and volume (especially for iodinated contrast materials that are administered intravenously); osmolality effects; potential transmetalation of complexes of gadolinium, manganese, or iron (generally MRI drugs); potential effects of tissue or cellular accumulation on organ function (particularly if the drug is intended to image a diseased human organ system); and the chemical, physiological, and physical effects of ultrasound microbubble drugs (e.g., coalescence, aggregation, margination, and cavitation).

2. Diagnostic Radiopharmaceuticals

Because of the characteristics of diagnostic radiopharmaceuticals and the way they are used, nonclinical safety evaluations of these drugs may be made more efficient by the following modifications:

- Long-term, repeat-dose toxicity studies in animals typically may be eliminated.
- Long-term rodent carcinogenicity studies usually may be omitted.
- Reproductive toxicology studies may generally be waived when adequate scientific justification is provided.¹⁶
- Waivers for the performance of genotoxicity studies may be granted when scientifically justified.¹⁷

¹⁴ See *S5A Detection of Toxicity to Reproduction for Medicinal Products* (ICH), September, 22, 1994, and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (ICH), April 5, 1996.

¹⁵ Waiver regulations for INDs are set forth at 21 CFR 312.10; those for NDAs appear at 21 CFR 314.90.

¹⁶ See ICH *S5A* and ICH *S5B*.

¹⁷ See *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH), April 24, 1996, and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (ICH), November 21, 1997.

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In reproductive toxicology and genotoxicity studies, components other than the radionuclide should be considered separately because they may be genotoxins or teratogens, causing effects that may exceed those of the radioactivity alone.

Special safety considerations for diagnostic radiopharmaceuticals may include verification of the mass dose of the radiolabeled moiety; assessment of the mass, toxic potency, and receptor interactions for any unlabeled moiety; evaluation of all components of the final formulation for toxicity potential (e.g., excipients, reducing drugs, stabilizers, anti-oxidants, chelators, impurities, residual solvents); and potential pharmacologic or physiologic effects due to molecules that bind with receptors or enzymes.

3. Timing of Nonclinical Studies Submitted to an IND Application

Appropriate timing of nonclinical studies should facilitate the timely conduct of clinical trials (including appropriate safety monitoring based upon findings in nonclinical studies) and should reduce the unnecessary use of animals and other resources.¹⁸ The recommended timing of nonclinical studies for medical imaging drugs is summarized below.

- a. Completed Before Phase 1:
 - Safety pharmacology studies. Particular emphasis should be placed on human organ systems in which the medical imaging drug localizes and on organ systems that the product is intended to visualize, especially if the organ system has impaired function.
 - Toxicokinetic and pharmacokinetic studies (see ICH guidances).
 - Single-dose toxicity studies. *Expanded acute* single-dose toxicity studies are strongly recommended.¹⁹ However, if short-term, repeated-dose toxicity studies have been completed, nonexpanded, single-dose toxicity studies may be sufficient.

¹⁸ See *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (ICH), November 25, 1997.

¹⁹ See *Single Dose Acute Toxicity Testing for Pharmaceuticals*, August 1996.

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- For medical imaging drugs that are administered intravenously: (1) local tolerance and irritancy studies, including evaluations of misadministration or extravasation, (2) blood compatibility studies, including evaluations of hemolytic effects, and (3) effects on protein flocculation.
- Radiation dosimetry, if applicable.
- In vitro genotoxicity studies (see Section VI.B.2 for diagnostic radiopharmaceuticals).

b. Completed Before Phase 2:

- Short-term, repeated-dose toxicity studies.
- Immunotoxicity studies.
- In vivo genotoxicity studies (see Section VI.B.2 for diagnostic radiopharmaceuticals).

c. Completed Before Phase 3:

Reproductive toxicity studies if needed (see Section VI.B.2 for diagnostic radiopharmaceuticals).

d. Completed No Later Than the End of Phase 3:

- Drug interaction studies.
- In vivo or in vitro studies that further investigate adverse effects seen in previous nonclinical studies.

VII. GENERAL CONSIDERATIONS IN THE CLINICAL EVALUATION OF MEDICAL IMAGING DRUGS

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Many considerations in the overall clinical development of drugs are summarized in ICH and FDA guidance documents.²⁰ The principles described in these documents also apply to the development of medical imaging drugs. These general developmental considerations include, but are not limited to, the demonstration of safety and efficacy; the procurement of adequate dose-response, pharmacodynamic, and pharmacokinetic data to support licensing; and special issues such as consideration of drug metabolites, drug-drug interactions, and special populations.

These documents also discuss issues of trial design, conduct, analysis, and reporting of individual clinical studies. The principles described in these documents apply to individual clinical studies of medical imaging drugs. Relevant topics include, but are not limited to, study objectives, study design, selection of subjects, dosage evaluation, selection of control groups, numbers of subjects, response variables (i.e., endpoints or outcome measures), methods of minimizing or assessing bias (e.g., by randomization and blinding), and issues in statistical analysis.

However, the development of medical imaging drugs for diagnostic purposes may also raise issues somewhat different from those raised during the development of therapeutic drugs. These issues deserve special attention. The following sections discuss some issues that are particularly relevant to medical imaging drug development. Considering them during the product development process may increase the efficiency of the clinical development of these products.

A. Phase 1 Studies²¹

Phase 1 studies can include, but are not limited to, assessments of the safety of single, increasing doses of a drug and evaluations of human pharmacokinetics. Depending upon the drug and its potential toxicities, these trials may begin in healthy volunteers or in patients. Screening for potential human toxicities may include serial evaluations of clinical laboratory tests (e.g., hematology, clinical chemistry, urinalysis), other laboratory tests (e.g., electrocardiograms), and adverse events. Pharmacokinetic evaluations should address the absorption, distribution, metabolism, and excretion of all components of the drug formulation and any metabolites. Sponsors are encouraged to consult with the appropriate FDA review division on pharmacokinetic issues. Evaluation of a medical imaging drug that targets a specific metabolic process or receptor should include assessments of the drug's potential effects on directly related functions.

²⁰ See ICH efficacy guidances available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>, or <http://www.fda.gov/cber/guidelines/index.htm>.

²¹ See also guidance for industry, *Content and Format of Investigational New Drug Applications (INDs) for Phase-1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*, November 1995.

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For diagnostic radiopharmaceuticals, organ/tissue distribution data over time should be collected to optimize subsequent imaging protocols and calculate radiation dosimetry (see Section XI.C). Whenever possible, pharmacokinetics and pharmacodynamic evaluations should be made not only for the diagnostic radiopharmaceutical itself, but also for the radionuclide and for the carrier or ligand. The effects of large doses of the diagnostic radiopharmaceutical (including the carrier or ligand and other vial contents) should usually be assessed. This can be achieved, for example, by administering large doses of the medical imaging drug with low specific activity, by administering the contents of an entire vial of the medical imaging drug (assuming that this approximates a worst-case scenario in clinical practice), or both.

B. Phase 2 Studies

Goals of Phase 2 studies of medical imaging drugs can include, but are not limited to, refining the product's clinically useful dose range or dosage regimen (e.g., bolus administration or infusion), answering outstanding pharmacokinetic and pharmacodynamic questions, providing preliminary evidence of efficacy, expanding the safety database, optimizing techniques and timing of image acquisition, and evaluating other critical concepts or questions about the drug.

Dose considerations include the following: adjustment of the character or amount of active and inactive ingredients, amount of radioactivity, amount of nonradioactive ligand or carrier, specific activity, and use of different radionuclides. Methods used to determine the comparability, superiority, or inferiority of different doses or regimens should be discussed with the Agency. To the extent possible, the formulation that will be used for marketing should be used in Phase 2 studies. When a different formulation is used, bioequivalence and other bridging studies may help document the relevance of data collected with the original formulation.

Phase 2 trials should be designed to define the appropriate patient populations for Phase 3 trials. To gather preliminary evidence of efficacy, however, both subjects with known disease (or patients with known structural or functional abnormalities) and subjects known to be normal for these conditions may be included in clinical studies. Methods, endpoints, and items on the case report form (CRF) that will be used in critical Phase 3 trials should be tested and refined.

C. Phase 3 Studies

The goals of Phase 3 efficacy studies typically are to confirm the principal hypotheses developed in earlier studies, demonstrate the efficacy and continued safety of the drug, and

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validate instructions for use and for imaging in the population for which the drug is intended. The design of Phase 3 studies (e.g., dosage, imaging techniques and times, patient population, and endpoints) should be based on the findings in Phase 2 trials. The to-be-marketed formulation should be used, or else bridging studies should be performed.

When multiple efficacy studies are performed, the studies may be of different designs.²² To increase the extent to which the results can be generalized, the studies should be independent of one another and should use different investigators, clinical centers, and readers that perform the *blinded* image evaluations (see Section VIII.B).

VIII. SPECIAL CONSIDERATIONS IN THE CLINICAL EVALUATION OF EFFICACY

The following sections describe special considerations for the evaluation of efficacy in clinical trials for medical imaging drugs.

A. Selection of Subjects

The subjects included in critical Phase 3 clinical studies should be representative of the population in which the medical imaging drug is intended to be used.

1. For claims (a) *structure delineation*, or (b) *functional, physiological, or biochemical assessment*, adequate numbers of subjects should be enrolled. The full range of severity of the structural or functional abnormality (e.g., from mild to severe disease, from early to advanced disease) should be appropriately represented. This is to provide adequate estimates of the validity and reliability of the medical imaging drug over the full range of conditions for which it is intended to be used. The spectrum of other conditions, processes, or diseases (e.g., inflammation, neoplasm, infection, trauma) that may confound interpretation of the results for the disease or condition of interest also should be appropriately represented.

Subject selection may be based on representative diseases that involve similar alterations in structure, function, physiology, or biochemistry if it appears that the results may be extrapolated to other unstudied disease states based on a known common process. Appropriate models should be selected on a case-by-case basis.

²² See guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998.

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Data to justify inclusion of a particular disease should be thoroughly documented, as should the data to support why the results obtained from the models can be extrapolated to other diseases.

Adequate numbers of normal or unaffected subjects should be enrolled during drug development in appropriately designed trials to establish the performance for the imaging drug in this population.

2. For claims (a) *disease or pathology detection or assessment*, or (b) *diagnostic or therapeutic patient management*, adequate numbers of subjects should be enrolled to demonstrate the validity and reliability of the information provided by the medical imaging drug. Because the validity and reliability of the medical imaging drug may vary depending on the characteristics of the patients and the clinical setting, the enrolled patients should be evaluated in defined clinical settings reflecting the proposed indications. For example, if a drug is to be used as a tool to aid in the diagnosis of patients *suspected* of having Alzheimer's disease, studies should not be limited to patients in which Alzheimer's disease is already *known* to be present or absent.

The pretest odds and pretest probabilities of disease should be estimated for all subjects to aid subsequent clinical use of the medical imaging drug. Whenever possible, these odds and probabilities should be derived from prespecified criteria of disease (e.g., history, physical findings, results of other diagnostic evaluations) according to prespecified algorithms.

B. Image Evaluations

Because of the many ways that imaging data may be acquired, reconstructed, processed, stored, and displayed and because of the diversity of imaging modalities, the following sections use the term *images* in a general way. *Images* include, but are not limited to, films, likenesses or other renderings of the body, body parts, organ systems, body functions, or tissues. Because of this heterogeneity, the general recommendations delineated below for image evaluation in clinical trials may need to be customized to be applied to a specific medical imaging drug or imaging modality. For example, an *image* of the heart obtained with a diagnostic radiopharmaceutical or an ultrasound contrast agent may in some cases refer to a *set* of images acquired from different views of the heart (e.g., short-axis and long-axis views). Similarly, an *image* obtained with an MRI contrast agent may in some cases refer to a *set* of images acquired with different pulse sequences and interpulse delay times.

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The specific ways that images will be acquired, reconstructed, processed, stored, displayed, and evaluated in clinical studies should be documented clearly in the study protocol. Special emphasis should be placed on the particulars of the blinded image evaluation. Study reports should reiterate much of this information and should highlight any differences from the protocol in the conduct of the study, including any changes in the execution of the blinded image evaluations.

1. Characteristics of the Readers

In studies that are intended to demonstrate efficacy of a medical imaging drug, evaluations of images should be performed by readers that are both *independent* and *blinded* (as defined below). Independent, blinded image evaluations may not be entirely representative of the conditions under which the test drug will ultimately be used clinically, but they compel the readers to rely on objective image features in their assessments of the effects of the drug. These independent, blinded image evaluations are intended to limit possible biases that could be introduced into the image evaluation by non-independent or unblinded readers.

Independent readers are those who have not otherwise participated in the Phase 3 studies (e.g., as investigators) and who are not otherwise affiliated with the sponsor or with institutions at which the studies were conducted.

Blinded readers are those who are unaware (1) of treatment identity (particularly in studies where images have been obtained with more than one treatment) and (2) of patient-specific clinical information or the study protocol. That is, in clinical studies of medical imaging drugs, blinded readers should be *blinded* in several ways, including ways that may not be encompassed by the usual definitions of the term in therapeutic clinical trials. First, blinded readers should be unaware of the identity of the treatment used to obtain a given image. This is the common meaning of blinding in therapeutic clinical trials.²³ For example, in a comparative study of two or more medical imaging drugs (or two or more doses or administration regimens), the blinded readers should not know about the identity of the drug (or dose or method of administration) used to obtain the particular image. For contrast agents, this also may include lack of knowledge about which images were obtained prior to drug administration and which were obtained after drug administration, although sometimes this may be apparent upon viewing the images.

²³ See *E8 General Considerations for Clinical Trials* (ICH), December 17, 1997, and *E9 Statistical Principles for Clinical Trials* (ICH), September 16, 1998.

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Second, blinded readers also should be unaware or have limited awareness of patient-specific clinical information or of the study protocol. Anatomic orientation to the images should be minimal. This meaning of *blinding* differs from the common way the term is used in therapeutic clinical trials. However, blinding in this sense is a critical aspect of clinical trials of medical imaging agents. For example, blinded readers should generally not have knowledge of the patients' final diagnoses and may have limited or no knowledge of the results of other diagnostic tests that were performed on the patients, including the results of other imaging studies. In some cases, blinded readers should not be familiar with the inclusion and exclusion criteria for patient selection that were specified in the protocol.

At least two independent, blinded readers (and preferably three or more) are recommended for each study that is intended to demonstrate efficacy. This provides a better basis for subsequent generalization of the findings in the studies. All images obtained in the study (i.e., not just those determined to be evaluable) should be read by the readers, including images of test patients, control patients, and normal subjects. Each reader should read the images independently of the other blinded readers and independently of any on-site readings performed by the investigators. Consistency among readers should be measured quantitatively (e.g., with the kappa statistic). Consensus reads may be done after the readings are completed, but should not be performed for primary efficacy evaluation of the test drug. Readers may be trained in scoring procedures using sample images from Phase 1 and Phase 2 studies. Meanings of all endpoints should be clearly understood for consistency.

Sequential unblinding (i.e., providing more and more clinical information to the readers) might be used to provide incremental information under a variety of conditions that may occur in routine clinical practice (e.g., when no clinical information is available, when limited clinical information is available, and when a substantial amount of information is available). This may be used to determine when or how the test drug should be used in a diagnostic algorithm.

2. Presentation of the Images to the Readers

Images may be presented to the readers in several ways. As described below, this image evaluation should usually consist of randomized readings that are separate, combined, or both. *Randomization* of images refers to merging the images obtained in the study (to the fullest degree that is practical) and then presenting images in this merged set to the readers in a random sequence. For example, when the efficacy of several diagnostic radiopharmaceuticals are being compared (e.g., a

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comparison of a test drug to an established drug), the readers should generally evaluate individual images from the merged set of images in a random sequence.:

a. Separate Image Evaluations

Separate image evaluations should generally be performed by independent, blinded readers in the efficacy evaluation of a medical imaging drug. Such image evaluations may not be entirely representative of the conditions under which the test drug will ultimately be used clinically. However, these conditions compel the readers to evaluate each image on its own merits, without reference to any other image, and help to limit possible biases that could be introduced into the image evaluation by a nonrandomized or combined image evaluation.

Separating images refers to segregating the images (to the fullest degree that is practical) from other images that were obtained in the same patient at different times or under different conditions. These segregated images can then be presented to the readers in random sequence so that images are not viewed simultaneously. For example, when both unenhanced and enhanced images are obtained as part of a study of a contrast drug product, the images obtained before administration of the contrast drug product (i.e., the *unenhanced* images) should generally be mixed with the images obtained after administration of the drug (i.e., the *enhanced* images). Individual images in this intermixed set should then be read in random sequence so that the unenhanced and enhanced images are not viewed simultaneously. Alternatively, in some cases, the individual unenhanced images may be evaluated in a random order, followed by an evaluation of the individual enhanced images in a random order. In settings where the unenhanced image will not be used in clinical practice, images should be evaluated in a separate fashion, to show, for example, that the information from the enhanced image, alone, is clinically and statistically superior to the information from the unenhanced image, alone.

b. Combined Readings

Combined readings by independent, blinded readers may also be useful in evaluating the efficacy of a medical imaging drug because this type of evaluation often resembles the conditions under which the drug will be

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used clinically.²⁴ *Combining* the images refers to simultaneous, or nearly simultaneous presentation to the reader of two or more images that were obtained at different times or under different conditions. Sets of combined images can then be presented to the readers in random sequence. For example, in studies of contrast drug products, both unenhanced and enhanced images may be obtained. The images, which were obtained at different times and under different conditions, may be viewed simultaneously by the reader. Similarly, for a diagnostic radiopharmaceutical, serial images may be obtained after drug administration to determine the optimal time for imaging. These images may be viewed in a combined fashion.

However, when this type of reading is performed, it is often advisable that an additional *separate* image evaluation be completed on at least one of the members of the combination. In this way, differences in the evaluations of the combined reading with those of the separate reading may be assessed. The combined images and the separate image may then be evaluated statistically with a paired comparison. For contrast drug products, these differences should demonstrate that the information from the combined images is clinically and statistically superior to information obtained from the unenhanced image alone. For example, if a combined image evaluation is performed in a two-dimensional study of blood vessels with a microbubble ultrasound contrast agent (e.g., evaluation of the unenhanced and enhanced images side by side or in close temporal proximity), another evaluation of the separate, unenhanced image of the blood vessel (i.e., images obtained with the device alone) may allow the microbubble effects on the image to be assessed.

These combined evaluations should be designed to minimize the likelihood that the readers will know (or be able to recall) their assessment of the separate image assessment (or vice versa). Thus, different pages in the CRF should be used for the combined and separate evaluations, and the combined and separate image evaluations should usually be performed at different times without reference to prior results.

When differences between the combined and separate images are to be assessed, the combined CRF and separate CRF should contain items or

²⁴ If a randomized, combined reading is the only evaluation that is done, labeling of the medical imaging drug (e.g., the INSTRUCTIONS FOR USE) should specify that combined evaluations should be performed in clinical practice.

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questions that are identical in order to allow differences to be calculated. For example, on the separate CRF for a contrast drug product seeking a structural delineation claim, the readers may be asked to rate the clarity of border delineation of a structure on an ordinal scale (e.g., 0, 1, 2, 3, 4). The combined CRF should ask the same question and the difference in grades could be calculated. The purpose of this approach is to minimize potential biases that may arise if the CRF contains only questions or items that ask for relative judgments to be made. If desired, however, additional comparative questions and items may be added to the combined pages in the CRF. For example, the readers may be asked to rate the relative clarity of border delineation in the second image compared to the first (e.g., better, same, worse).

C. Truth Standards (*Gold Standards*)

A truth standard provides an independent way of evaluating the same variable being assessed by the investigational drug. A truth standard is known or believed to give the true state of a patient or true value of a measurement. Truth standards are used to demonstrate that the results obtained with the medical imaging drug are valid and reliable.

1. To minimize potential bias, determination of the true state of the subjects (e.g., diseased or nondiseased) with a truth standard should be performed without knowledge of the test results obtained with the medical imaging drug or test agent.
2. For contrast drug products, the results of the unenhanced images should generally not be incorporated in the truth standard. This is to decrease possible spurious correlations that may result from an imaging modality *agreeing with itself*. Stated differently, the truth standard should provide an assessment of disease status that is *independent* of the imaging modality for which the medical imaging drug is intended. For example, for a CT contrast agent intended to visualize abdominal masses, unenhanced abdominal CT images generally should not be included in the truth standard. However, components of the truth standard might include results from other imaging modalities (e.g., MRI, ultrasonography).

From a practical perspective, diagnostic standards are derived from procedures that are considered more definitive in approximating the truth than the test drug. For example, histopathology or long-term clinical outcomes may be acceptable diagnostic standards for determining whether a mass is malignant. Diagnostic

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standards may not be error free, but for purposes of the clinical trial, they are regarded as definitive. The choice of the standard should be discussed with the Agency during design of the clinical trials to ensure that it is appropriate.

As noted in the proposed rule for diagnostic radiopharmaceuticals, a valid assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated validity. In the absence of such diagnostic standards, the actual clinical status may in some cases be established in another manner, e.g., through patient follow-up. However, when a suitable diagnostic standard is unavailable or cannot be assessed practically, consideration should be given to changing the focus of the study to evaluate the effects of the product on clinical outcomes (see Section IV.D.4).

Truth standards may be other diagnostic tests (e.g., tissue biopsy to evaluate whether a mass is malignant) or appropriate combinations of other clinical data and diagnostic tests. For example, a definitive determination about whether a patient enrolled in a clinical trial experienced an acute myocardial infarction could be obtained by evaluating the combination of patient history (e.g., nature and location of pain), 12-lead electrocardiogram (e.g., Q waves or not), and serum levels of cardiac enzymes (e.g., creatine phosphokinase) according to a prespecified algorithm. Using these data, a panel of experts that is blinded to the medical imaging results yielded by the test agent could then make the definitive determination about the presence or absence of disease (i.e., an acute myocardial infarction).

D. Controls

As in other adequate and well-controlled clinical studies, clinical trials of medical imaging drugs may be controlled for different purposes and in a number of different ways. Before selecting the controls, discussions with the Agency are strongly recommended.

1. Comparison to Establish Performance in Relationship to a Drug or Modality Approved for a Similar Indication

In the event that the test drug is being developed as an advance over an approved drug or other diagnostic modality, a direct, concurrent comparison to the approved comparator should be performed. The comparison should include an evaluation of both the safety and the efficacy data for the comparator and the test drug. Information from both test and control images should be compared not only to one another but also to an independent truth standard. This will facilitate an

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assessment of possible differences between the test drug and the comparator and will complete the assessment of diagnostic validity (e.g., sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios) between the two. Note that two medical imaging drugs could have similar values for sensitivity and specificity in the same set of patients, yet have poor agreement rates with each other. Similarly, two medical imaging drugs could have good agreement rates, yet both have poor sensitivity and specificity values.

When a medical imaging drug is being developed for an indication for which other drugs or diagnostic modalities have been approved, a direct, concurrent comparison to the approved drug or diagnostic modality is encouraged. However, prior approval of a drug for use in a particular indication does not necessarily mean that the results of a test with that drug may be used as a truth standard. Note that For example, if a medical imaging drug has been approved on the basis of sufficient concordance of findings with truth as determined by histopathology, assessment of the new drug should also usually include determination of truth by histopathology.

2. Placebos

Whether the use of a placebo is appropriate in the evaluation of a medical imaging drug depends upon the specific drug, proposed indication, and imaging modality. In some cases, the use of placebos may help minimize potential bias in the conduct of the study, and may facilitate unambiguous interpretation of efficacy or safety data. However, in some diagnostic studies (such as ultrasonography), products that are generally considered as placebos (e.g., water, saline, or the test drug vehicle) can have some diagnostic effects. These should be used as controls to demonstrate that the medical imaging drug has an effect above and beyond that of the vehicle.

E. Endpoints

In the evaluation of images, objective, quantifiable endpoints should be used whenever possible (e.g., signal-to-noise ratios, delineation, opacification; size of lesion, number of lesions, density of lesions). These endpoints may be complemented by other endpoints that ask the blinded readers to *interpret* the meaning of the objective image features (e.g., to make an assessment about whether a mass is malignant or benign). For example, data on a lesion's features may be complemented with additional assessments that demonstrate the impact of the drug on the physician's diagnosis.

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Imaging CRFs should be designed to capture imaging endpoints, including technical features of the images as well as the location of, and interpretation of, findings. Subjective interpretations of findings should be supported by objective quantitative or qualitative information derived from the images. Items on the CRF should be carefully constructed to gather information without introducing a bias that indicates the answer that is being sought.

The proposed labeled indication should be clearly derived from specific items in the CRF and from endpoints and hypotheses that have been prospectively stated in the protocol.

IX. ISSUES IN IMAGE ACQUISITION AND HANDLING

A. Image Acquisition

In studies that compare the effects of a test drug with another drug or imaging modality, images taken before study enrollment with the comparator drug or modality should not be used to determine whether a patient is enrolled in the study. These images also should not be part of the database used to determine test drug performance. Such baseline enrollment images have inherent selection bias because they are unblinded and based on referral and management preferences. All images used to determine the efficacy of the test drug and the comparator drug (or imaging modality) should be taken after study enrollment and within a time frame when the disease process is expected to be the same.

B. Image Handling Procedures

Ideally, all images should be evaluated by the blinded readers. In some cases where large numbers of images are obtained or where image tapes are obtained (e.g., cardiac echocardiography), sponsors have used image selection procedures. This is strongly discouraged because the selection of images can introduce the bias of the selector. In cases where preselection is thought to be needed, the sponsor is encouraged to clearly identify and discuss the selection procedures with the appropriate Agency division before their implementation.

X. STUDY ANALYSIS

Many imaging agent trials are designed to provide dichotomous or ordered categorical outcomes, and it is important that appropriate assumptions and statistical methods be applied in their analysis. Statistical tests for proportions and rates are commonly used for dichotomous

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outcomes, and methods based on ranks are often applied to ordinal data. Additional analyses based on odds ratios can provide further insight. Study outcomes can often be stratified in a natural way, such as by center or other subgroup category, and the Mantel-Haenszel²⁵ procedures provide effective ways to examine both binomial and ordinal data. Exact methods of analysis, based on conditional inference, should be employed when necessary. The use of model-based methods should also be encouraged. These techniques include logistic regression models for binomial data and proportional odds models for ordinal data. Log-linear models can be used to evaluate nominal outcome variables.

Dichotomous outcomes in studies that compare images obtained after the test drug to images obtained before the test drug are often analyzed as matched pairs, where differences in treatment effects can be assessed by using methods for correlated binomial outcomes. These studies, however, may be problematic because they often do not employ blinding and randomization. For active- and placebo-control studies, including dose-response studies, crossover designs can often be used to gain efficiency. It is important that subjects are randomized to order of treatment. If subjects are not randomized to order of treatment, a crossover analysis applied to the images may still be informative. Study results from a crossover trial should always be analyzed with methods specifically designed for such trials.

Diagnostic validity can be assessed in a number of ways. With pre- and post-images, for example, each could be compared to the truth standard, and the sensitivity and specificity of the pre-image compared to that of the post-image. Two different active agents can be compared similarly. Diagnostic comparisons can also be made when there are more than two outcomes to the diagnostic test results. Common methods used to test for differences in diagnosis include the McNemar test and the Stuart Maxwell test.²⁶ In addition, confidence intervals for sensitivity, specificity, and other measures should be provided in the analyses. Receiver operating characteristic (ROC) analysis is another approach that can be used to evaluate diagnostic accuracy.

XI. CLINICAL SAFETY ASSESSMENTS²⁷

²⁵ For more on this topic, see Fleiss, Joseph, L., *Statistical Methods for Rates and Proportions*, 2nd ed., 1981, John Wiley and Sons, New York; and Woolson, Robert, *Statistical Methods for the Analysis of Biomedical Data*, 1987, John Wiley and Sons, New York.

²⁶ Ibid.

²⁷ See also guidance for industry and reviewers, *Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs, and Biologics*, March 18, 1998; and the final rule, "Expedited Safety Reporting Requirements for Human Drug and Biological Products," October, 7, 1997 (62 FR 52237).

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Clinical safety assessments of both contrast drug products and diagnostic radiopharmaceuticals may be tailored based on their characteristics (e.g., dose, route of administration, frequency of use, and biological half-life), on the results of nonclinical safety assessments, and on the results of clinical pharmacokinetic/biopharmaceutics studies.

This guidance defines two categories of medical imaging drugs: Group 1 and Group 2. The extent of clinical safety monitoring and evaluation differs for these two categories. Medical imaging drugs classified as *Group 1 medical imaging drugs* may be able to undergo a more efficient clinical safety evaluation during development. *Group 2 medical imaging drugs* should undergo a complete clinical safety evaluation. Both Group 1 and 2 diagnostic radiopharmaceuticals should undergo complete radiation dosimetry assessments.²⁸ Preliminary categorization of medical imaging drugs into one of these two groups may be based on findings in nonclinical studies.

A. Group 1 Medical Imaging Drugs

Group 1 medical imaging drugs have been shown to be biologically inactive in nonclinical studies and to have undetectable levels of biological activity in human studies when administered at dosages that are similar to those intended for clinical use. Group 1 diagnostic radiopharmaceuticals are a subset of this group.^{29, 30}

To be included in Group 1, a medical imaging drug should have the following:

1. An adequately documented margin of safety between nonclinical and clinical use. The no-observable-effect level (NOEL),³¹ as appropriately adjusted in suitable

²⁸ See Section XI.C.

²⁹ This classification conforms with the proposed rule for diagnostic radiopharmaceuticals, which states that diagnostic radiopharmaceuticals may be categorized based on defined characteristics related to their risk.

³⁰ Group 1 diagnostic radiopharmaceuticals may include radionuclides, ligands, and carriers that are known to be biologically inactive. This group may include radionuclides, ligands, and carriers used at radiation doses or mass dosages that are similar to, or less than, those used previously. This group also may include radionuclides, ligands, and carriers that have been documented not to produce adverse reactions.

³¹ In this guidance, the *no-observable-effect level* is defined as the dosage level of a medical imaging drug at which no biological effects are observed. These biological effects include, but are not limited to, those that are biochemical, physiologic, pharmacologic, or structural. These biological effects do not necessarily have to be adverse or *toxic*. Adverse and toxic effects should be evaluated in the most susceptible species with the most sensitive assay. For purposes of this guidance, *localization* of a medical imaging drug in a target organ or target tissue (e.g., by binding to a

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animal species, should be at least one thousand times greater than the maximal dose and dosage to be used in human studies. To establish this margin of safety the NOEL should be determined in each of the following nonclinical studies:

- a. expanded-acute, single-dose toxicity studies
- b. short-term, repeated-dose toxicity studies
- c. safety pharmacology studies

Appropriately adjusted means that dosage comparisons between animals and humans are suitably modified for factors such as body size (e.g., body surface area) and otherwise adjusted for possible pharmacokinetic and toxicokinetic differences between animals and humans (e.g., differences in absorption for products that are administered orally).

2. Completed and fully documented Phase 1 clinical trial experience in appropriately designed trials that are consistent with the animal data. The medical imaging drug should not demonstrate any biological activity in human trials. The human pharmacokinetic trials also should provide data that allow adequate comparisons of exposure to be made between humans and the animal species used in the nonclinical studies.

Alternatively, to be included in Group 1, a medical imaging drug should have a history of sufficient clinical use or of previous clinical trial experience that adequately documents the following:

- a. No clinically detectable allergic, immunologic, biochemical, physiologic, or pharmacologic responses at clinical doses or dosages; and
- b. No known dose-related toxicological risk or adverse event profile at clinical doses or dosages.

For Group 1 medical imaging drugs, reduced safety monitoring in Phases 2 and 3 of drug development is justified. However, if toxicity is noted during clinical development, appropriate clinical safety monitoring should be performed.

B. Group 2 Medical Imaging Drugs

tissue receptor) is by itself not considered to be a biological effect, unless it produces demonstrable perturbations.

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Group 2 medical imaging drugs have been shown to be biologically active in animal studies or in human studies when administered at dosages that are similar to those intended for clinical use. Group 2 diagnostic radiopharmaceuticals are a subset of this group.³²

Group 2 medical imaging drugs include the following:

1. Any medical imaging drug that does not meet the criteria for a Group 1 medical imaging drug;
2. All biological medical imaging drugs;^{33,34}
3. Any diagnostic radiopharmaceutical containing a radionuclide that undergoes alpha or beta decay.

For Group 2 medical imaging drugs, standard safety evaluations and monitoring should be performed in clinical trials.

C. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals³⁵

Radiation safety assessments should be documented for both Group 1 and Group 2 diagnostic radiopharmaceuticals. The radiation safety assessment should establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation should consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. The radiation doses of diagnostic radiopharmaceuticals should be kept as low as reasonably achievable (ALARA). The maximum tolerated radiation dose need not be

³² Group 2 diagnostic radiopharmaceuticals may also include radionuclides and carriers that are known to be biologically active. This group includes radionuclides and carriers used at radiation doses or mass dosages that are higher than those used previously, including radionuclides and carriers that have been documented to produce adverse reactions.

³³ Biological medical imaging products, such as radiolabeled monoclonal antibodies or monoclonal antibody fragments, are classified within Group 2 because of their potential to elicit immunologic responses.

³⁴ See also the final rule, "Adverse Experience Reporting Requirements for Licensed Biological Products," October 27, 1994 (59 FR 54042).

³⁵ This section is based largely on the radiation dosimetry section of *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*. February 27, 1997.

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established. For diagnostic radiopharmaceuticals, estimates of the organ dosimetry should be performed in animals prior to the first Phase 1 study. Phase 1 studies of diagnostic radiopharmaceuticals should include studies that will obtain sufficient data for dosimetry calculations (21 CFR 312.23(a)(10)(ii)).

1. General Considerations

An IND sponsor should submit sufficient data from animal or human studies to allow a reasonable calculation of radiation absorbed dose to the whole body and to critical organs upon administration to a human subject (21 CFR 312.23(a)(10)(ii)). The following organs and tissues should be included in dosimetry estimates: (1) all target organs/tissues; (2) bone; (3) bone marrow; (4) liver; (5) spleen; (6) adrenal glands; (7) kidney; (8) lung; (9) heart; (10) urinary bladder; (11) gall bladder; (12) thyroid; (13) brain; (14) gonads; (15) gastrointestinal tract; and (16) adjacent organs of interest.

The amount of radiation delivered by internal administration of diagnostic radiopharmaceuticals should be calculated by internal radiation dosimetry. The absorbed fraction method of radiation dosimetry has been described by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and the International Commission on Radiological Protection (ICRP) (see also 21 CFR 361.1 (b)(3)(iv)).

The methodology used to assess radiation safety should be specified. The mathematical equations used to derive the radiation doses and the absorbed dose estimates should be provided along with a full description of assumptions that were made. Sample calculations and all pertinent assumptions should be listed and submitted.

Safety hazards for patients and health care workers during and after administration of the radiolabeled antibody should be identified, evaluated, and managed appropriately.

2. Calculation of Radiation Dose to the Target Organ(s) or Tissue(s)

The following items should be determined based on the average patient:

- a. The amount of radioactivity that accumulates in the target tissue(s) or organ(s).

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- b. The amount of radioactivity that accumulates in tissues adjacent to the target tissue(s) or organ(s).
- c. The residence time of the diagnostic radiopharmaceutical in the target tissue(s) or organ(s) and in adjacent regions.
- d. The radiation dose from the radionuclide, including the free radionuclide and any daughter products generated by decay of the radionuclide.
- e. The total radiation dose from bound, free, and daughter radionuclides associated with the diagnostic radiopharmaceutical, based upon immediate administration following preparation and upon delayed administration at the end of the allowed shelf life.

3. Maximum Absorbed Radiation Dose

The amount of radioactive material administered to human subjects should be the smallest radiation dose that is practical to perform the procedure without jeopardizing the benefits obtained.

- a. The amount of radiation delivered by the internal administration of diagnostic radiopharmaceuticals should be calculated by internal radiation dosimetry using both the MIRD and ICRP methods. When making the radiation dosimetry safety assessment, the higher calculation of the two should be used.
- b. Because of known or expected toxicities associated with radiation exposure, dosimetry estimates should be obtained as described above.
- c. Calculations should anticipate possible changes in dosimetry that might occur in the presence of diseases in organs that are critical in metabolism or excretion of the diagnostic radiopharmaceutical. For example, renal dysfunction may cause a larger fraction of the administered dose to be cleared by the hepatobiliary system (or vice versa).
- d. Possible changes in dosimetry resulting from patient-to-patient variations in antigen or receptor mass should be considered in dosimetry calculations. For example, a large tumor mass may result in a larger than expected radiation dose to a target organ from a diagnostic radiopharmaceutical that has specificity for a tumor antigen.

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- e. The mathematical equations used to derive the estimates of the radiation dose and the absorbed dose should be provided along with a full description of assumptions that were made. Sample calculations and all pertinent assumptions should be listed.

- f. Calculations of dose estimates should be performed assuming freshly labeled material (to account for the maximum amount of radioactivity) as well as the maximum shelf life of the diagnostic radiopharmaceutical (to allow for the upper limit of radioactive decay contaminants). These calculations should (1) include the highest amount of radioactivity to be administered; (2) include the radiation exposure contributed by other diagnostic procedures such as roentgenograms or nuclear medicine scans that are part of the study; (3) be expressed as gray (Gy) per megabecquerel (MBq) or per millicurie (mCi) of radionuclide; and (4) be presented in a tabular format and include doses of individual absorbed radiation for the target tissues or organs and the organs listed above in section XI.C.1.

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GLOSSARY

Note: Subjects in trials of medical imaging agents may often be classified into one of four groups depending on (1) whether disease is present (often determined with a truth standard or *gold standard*) and (2) the results of the diagnostic test of interest (positive or negative). The following table identifies the variables that will be used in the definitions.

Test Result:	Disease:		
	Present (+)	Absent (-)	
Positive (+)	a true positive	b false positive	$m1 = a + b$ total with positive test
Negative (-)	c false negative	d true negative	$m2 = c + d$ total with negative test
	$n1 = a + c$ total with disease	$n2 = b + d$ total without disease	$N = a + b + c + d$ total in study

Accuracy: A measure of how faithfully the information obtained using a medical imaging agent reflects reality or *truth* as measured by a truth standard or *gold standard*. Accuracy is the proportion of cases, considering both positive and negative test results, for which the test results are correct (i.e., concordant with the truth standard or *gold standard*). Accuracy = $(a+d)/N$.

Likelihood ratio: A measure that can be interpreted either as (a) the relative *odds* of a diagnosis, such as being diseased or nondiseased, for a given test result, or (b) the relative *probabilities* of a given test result in subjects with and without the disease. This latter interpretation is analogous to a relative risk or risk ratio.

1. For tests with dichotomous results (e.g., positive or negative test results), the likelihood ratio of a positive test result may be expressed as LR(+), and the likelihood of a negative test result may be expressed as LR(-). See equations below.
2. For tests with several levels of results (e.g., tests with ordinal results), the likelihood ratio may be used to compare the proportions of subjects with and without the disease at each level of the test result.

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$$LR(+)=\frac{\frac{a}{n1}}{\frac{b}{n2}}=\frac{\text{sensitivity}}{1-\text{specificity}}=\frac{\text{TruePositiveRate}}{\text{FalsePositiveRate}}=\frac{\frac{a}{b}}{\frac{n1}{n2}}=\frac{\text{PostTestOdds}(+)}{\text{PreTestOdds}}$$

$$LR(-)=\frac{\frac{c}{n1}}{\frac{d}{n2}}=\frac{1-\text{sensitivity}}{\text{specificity}}=\frac{\text{FalseNegativeRate}}{\text{TrueNegativeRate}}=\frac{\frac{c}{d}}{\frac{n1}{n2}}=\frac{\text{PostTestOdds}(-)}{\text{PreTestOdds}}$$

LR(+): *Interpreted as relative odds:* LR(+) is the post-test odds of the disease (among those with a positive test result) compared to the pretest odds of the disease.

Interpreted as relative probabilities: LR(+) is the probability of a positive test result in subjects with the disease compared to the probability of a positive test result in subjects without the disease.

LR(-): *Interpreted as relative odds:* LR(-) is the post-test odds of the disease (among those with a negative test result) compared to the pretest odds of the disease.

Interpreted as relative probabilities: LR(-) is the probability of a negative test result in subjects with the disease compared to the probability of a negative test result in subjects without the disease.

Negative predictive value: The probability that a subject does not have the disease given that the test result is negative. Synonyms include *predictive value negative*. Negative predictive value = $d/m2$.

Odds: The probability that an event will occur compared to the probability that the event will not occur. For dichotomous events (e.g., for test results that are either positive or negative), the odds are defined as follows: Odds = (probability of the event)/(1 - probability of the event).

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Odds ratio: A measure of the amount of association between the presence or absence of disease and the diagnostic test results. Synonyms include *cross-product ratio*.

$$\text{OddsRatio} = \frac{\frac{a}{m1}}{\frac{b}{m2}} = \frac{\frac{a}{n1}}{\frac{c}{n2}} = \frac{a \cdot n2}{b \cdot m2}$$

Positive predictive value: The probability that a subject has disease given that the test result is positive. Synonyms include *predictive value positive*. Positive predictive value = $a/m1$.

Post-test odds of disease: The odds of disease in a subject after the diagnostic test results are known. Synonyms include *posterior odds of disease*. For subjects with a positive test result, the post-test odds of disease = a/b . For subjects with a negative test result, the post-test odds of disease = c/d . The following expression shows the general relationship between the post-test odds and the likelihood ratio: Post-test odds of disease = Pretest odds of disease x Likelihood ratio.

Post-test probability of disease: The probability of disease in a subject after the diagnostic test results are known. Synonyms include *posterior probability of disease*. For subjects with a positive test result, the post-test probability of disease = $a/m1$. For subjects with a negative test result, the post-test probability of disease = $c/m2$.

Precision: A measure of the reproducibility of a test, including reproducibility within and across drug doses, rates of administration, routes of administration, timings of imaging after drug administration, instruments, instrument operators, patients, and image interpreters, and possibly other variables. Precision is usually expressed in terms of variability, using such measures as confidence intervals and/or standard deviations. Precise tests have relatively narrow confidence intervals (or relatively small standard deviations).

Pretest odds of disease: The odds of disease in a subject before doing a diagnostic test. Synonyms include *prior odds of disease*. Pretest odds of disease = $n1/n2$.

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Pretest probability of disease: The probability of disease in a subject before doing a diagnostic test. Synonyms include *prevalence of disease* and *prior probability of disease*. Pretest probability of disease = $n1/N$.

Probability: The likelihood of occurrence of an event, expressed as a number between 0 and 1 (inclusive).

Sensitivity: The probability that a test result is positive given the subject has the disease. Synonyms include *true positive rate*. Sensitivity = $a/n1$.

Specificity: The probability that a test result is negative given that the subject does not have the disease. Synonyms include *true negative rate*. Specificity = $d/n2$.

Truth standard (gold standard): An independent method of measuring the same variable being measured by the investigational drug that is known or believed to give the *true* value of the measurement.

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whichever occurs later, and thereafter at intervals not to exceed 3,000 landings, inspect the wing front attachments (both the wing sides and fuselage sides) in accordance with Socata Service Bulletin No. SB 10-081-57, Amendment 1, dated August 1996.

(b) For all affected airplanes, accomplish the following on the wing front attachments on the wing sides:

(1) If no cracks are found on the wing front attachments on the wing sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 6,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 911000 in accordance with Socata Technical Instruction No. 9110, which incorporates the following pages:

Pages	Revision level	Date
0 and 1	Amendment	January 31, 1992.
2 through 11	Original Issue	October 1985.

(2) If a crack(s) is found on the wing front attachments on the wing sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 911000 in accordance with Socata Technical Instruction No. 9110. Incorporate this kit at intervals not to exceed 6,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(c) For Models TB9 and TB10 airplanes, with a serial number in the range of 1 through 399, or with a serial number of 413; that do not have either Socata Service Letter (SL) 10-14 incorporated or Socata Modification Kit OPT10 908100 incorporated, accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 6,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198-53, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198-53, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(d) For Models TB9 and TB10 airplanes, with a serial number in the range of 1 through 399, or with a serial number of 413; that have either Socata Service Letter (SL) 10-14 incorporated or Socata Modification Kit OPT10 908100 incorporated, accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198-53, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 919800 in accordance with Socata Technical Instruction of Modification OPT10 9198-53, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

(e) For Models TB9 and TB10 airplanes, with a serial number in the range of 400 through 412, or with a serial number in the range of 414 through 9999; accomplish the following on the wing front attachments on the fuselage sides:

(1) If no cracks are found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, upon accumulating 12,000 landings on these wing front attachments or within the next 100 landings after the effective date of this AD, whichever occurs later, and thereafter at intervals not to exceed 12,000 landings provided no cracks are found during any inspection required by paragraph (a) of this AD, incorporate Modification Kit OPT10 908100 in accordance with Socata Technical Instruction of Modification OPT10 9181-53, Amendment 2, dated October 1994.

(2) If a crack(s) is found on the wing front attachments on the fuselage sides during any inspection required by paragraph (a) of this AD, prior to further flight, incorporate Modification Kit OPT10 908100 in accordance with Socata Technical Instruction of Modification OPT10 9181-53, Amendment 2, dated October 1994. Incorporate this kit at intervals not to exceed 12,000 landings thereafter provided no cracks are found during any inspection required by paragraph (a) of this AD.

Note 3: "Unless already accomplished" credit may be used if the kits that are required by paragraphs (c)(1), (d)(1), and (e)(1) of this AD are already incorporated on the applicable airplanes. As specified in the AD, repetitive incorporation of these kits would still be required at intervals not to exceed 12,000 landings provided no cracks are found.

(f) Special flight permits may be issued in accordance with sections 21.197 and 21.199

of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

(g) An alternative method of compliance or adjustment of the initial or repetitive compliance times that provides an equivalent level of safety may be approved by the Manager, Small Airplane Directorate, FAA, 1201 Walnut, suite 900, Kansas City, Missouri 64106. The request shall be forwarded through an appropriate FAA Maintenance Inspector, who may add comments and then send it to the Manager, Small Airplane Directorate.

Note 4: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Small Airplane Directorate.

(h) Questions or technical information related to the service information referenced in this AD should be directed to the SOCATA—Groupe AEROSPATIALE, Socata Product Support, Aeroport Tarbes-Ossun-Lourdes, B P 930, 65009 Tarbes Cedex, France; telephone: 33-5-62-41-76-52; facsimile: 33-5-62-41-76-54; or the Product Support Manager, SOCATA Aircraft, North Perry Airport, 7501 Pembroke Road, Pembroke Pines, Florida 33023; telephone: (954) 893-1400; facsimile: (954) 964-1402. This service information may be examined at the FAA, Central Region, Office of the Regional Counsel, Room 1558, 601 E. 12th Street, Kansas City, Missouri.

Note 5: The subject of this AD is addressed in French AD 94-264(A), dated December 7, 1994.

Issued in Kansas City, Missouri, on May 14, 1998.

Michael Gallagher,

Manager, Small Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98-13653 Filed 5-21-98; 8:45 am]

BILLING CODE 4910-13-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 315 and 601

[Docket No. 98N-0040]

Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA), in response to the requirements of the Food and Drug Administration Modernization Act of 1997 (FDAMA), is proposing to amend the drug and biologics regulations by adding provisions that would clarify the evaluation and approval of in vivo

radiopharmaceuticals used in the diagnosis or monitoring of diseases. The proposed regulations would describe certain types of indications for which FDA may approve diagnostic radiopharmaceuticals. The proposed rule also would include criteria that the agency would use to evaluate the safety and effectiveness of a diagnostic radiopharmaceutical under the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act (the PHS Act).

DATES: Submit comments on this proposed rule on or before August 5, 1998. Submit written comments on the information collection provisions by June 22, 1998. See section IV of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Submit comments of the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Dano B. Murphy, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210; or Brian L. Pendleton, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5649.

SUPPLEMENTARY INFORMATION:

I. Introduction

Radiopharmaceuticals are used for a wide variety of diagnostic, monitoring, and therapeutic purposes. Diagnostic radiopharmaceuticals are used to image or otherwise identify an internal structure or disease process, while therapeutic radiopharmaceuticals are used to effect a change upon a targeted structure or disease process.

The action of most radiopharmaceuticals is derived from two components: A nonradioactive delivery component, i.e., a carrier and/or ligand; and a radioactive imaging component, i.e., a radionuclide. Nonradioactive delivery ligands and carriers are usually peptides, small proteins, or antibodies. The purpose of ligands and carriers is to direct the radionuclide to a specific body location or process. Once a radiopharmaceutical has reached its targeted location, the radionuclide component can be

detected. The imaging component usually is a short-lived radioactive molecule that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. The emitted photons are detected by specialized devices that generate images of, or otherwise detect, radioactivity, such as nuclear medicine cameras and radiation detection probe devices.

On November 21, 1997, the President signed FDAMA into law. Section 122(a)(1) of FDAMA directs FDA to issue proposed and final regulations on the approval of diagnostic radiopharmaceuticals within specific timeframes. As defined in section 122(b) of FDAMA, a radiopharmaceutical is an article "that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans * * * that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons[,] or * * * any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article." Section 122(a)(1)(A) of FDAMA states that FDA regulations will provide that, in determining the safety and effectiveness of a radiopharmaceutical under section 505 of the act (for a drug) (21 U.S.C. 355) or section 351 of the PHS Act (for a biological product) (42 U.S.C. 262), the agency will consider the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component), and the estimated absorbed radiation dose of the radiopharmaceutical.

FDAMA requires FDA to consult with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry before proposing any regulations governing the approval of radiopharmaceuticals. Accordingly, in the **Federal Register** of February 2, 1998 (63 FR 5338), FDA published a notification of a public meeting entitled "Developing Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring." The notice invited all interested persons to attend the meeting, scheduled for February 27, 1998, and to comment on how the agency should regulate radiopharmaceuticals. In particular, FDA invited comment on the following topics: (1) The effect of the use of a radiopharmaceutical in the practice of medicine on the nature and extent of safety and effectiveness evaluations; (2) the general characteristics of a radiopharmaceutical that should be

considered in the preclinical and clinical pharmacological and toxicological evaluations of a radiopharmaceutical (including the radionuclide as well as the ligand and carrier components); (3) determination and consideration of a radiopharmaceutical's estimated absorbed radiation dose in humans; and (4) the circumstances under which an approved indication for marketing might refer to manifestations of disease (biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.

Approximately 50 individuals from industry, academic institutions, professional medical organizations, and patient advocacy groups attended the February 27, 1998, public meeting and/or submitted comments in response to the notice. FDA has considered all of these comments in drafting this proposed rule.

The proposed rule applies to the approval of in vivo radiopharmaceuticals (both drugs and biologics) used for diagnosis and monitoring. The proposed regulations will not apply to radiopharmaceuticals used for therapeutic purposes. The regulations include a definition of diagnostic radiopharmaceuticals (which includes radiopharmaceuticals used for monitoring) and provisions that address the following aspects of diagnostic radiopharmaceuticals: (1) General factors to be considered in determining safety and effectiveness, (2) possible indications for use, (3) evaluation of effectiveness, and (4) evaluation of safety.

To establish these regulations, FDA proposes to add a new part 315 to title 21 of the Code of Federal Regulations (CFR) and to rename subpart D and add §§ 601.30 through 601.35 in part 601 (21 CFR part 601). These new provisions would complement and clarify existing regulations on the approval of drugs and biologics in parts 314 (21 CFR parts 314) and 601, respectively. In addition to these regulatory changes, FDA is in the process of revising and supplementing its guidance to industry on product approval and other matters related to the regulation of diagnostic radiopharmaceutical drugs and biologics. This guidance will address the application of the proposed rule. FDA will make such guidance available in draft form for public comment in accordance with the agency's Good Guidance Practices (see 62 FR 8961, February 27, 1997).

Positron emission tomography (PET) drugs are a particular type of radiopharmaceutical. Section 121 of FDAMA addresses these products

separately from other diagnostic radiopharmaceuticals and requires FDA to develop appropriate approval procedures and current good manufacturing practice requirements for PET products within the next 2 years. Although FDA expects the standards for determining the safety and effectiveness of diagnostic radiopharmaceuticals set forth in this proposed rule to apply to PET diagnostic products under the approval procedures that FDA intends to develop for those products, the agency will address this issue when it publishes its proposal on PET drugs.

II. Description of the Proposed Rule

The proposed rule would add a new part 315 to the CFR containing provisions on radiopharmaceutical drugs subject to section 505 of the act that are used for diagnosis and monitoring. Corresponding provisions applicable to radiopharmaceutical biological products subject to licensure under section 351 of the PHS Act would be set forth in revised subpart D of part 601. Both proposed regulations are discussed in the following section of this document.

A. Scope

Proposed §§ 315.1 and 601.30 define the scope of the diagnostic radiopharmaceutical provisions, i.e., that they apply only to radiopharmaceuticals used for diagnosis and monitoring and not to radiopharmaceuticals intended for therapeutic uses. FDA intends that these regulations will apply only to diagnostic radiopharmaceuticals that are administered in vivo. In vitro diagnostic products generally are regulated as medical devices under the act, although they may also be biological products subject to licensure under section 351 of the PHS Act (see 21 CFR 809.3(a)).

Some radiopharmaceuticals may have utility as both diagnostic and therapeutic drugs or biologics. When a particular radiopharmaceutical drug or biologic is proposed for both diagnostic and therapeutic uses, FDA will evaluate the diagnostic claims under the provisions in part 315 (for drugs) or subpart D of part 601 (for biologics) and evaluate the therapeutic claims under the regulations applicable to other drug or biologic applications.

B. Definition

The proposed ruling in §§ 315.2 and 601.31 would include a definition of "diagnostic radiopharmaceutical" that is identical to the definition of "radiopharmaceutical" in section 122(b) of FDAMA. Thus, a "diagnostic radiopharmaceutical" would be defined

as an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article. FDA interprets "disease or a manifestation of a disease" to include conditions that may not ordinarily be considered diseases, such as essential thrombocytopenia and bone fractures. In addition, FDA interprets the definition as including articles that exhibit spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons.

C. General Factors Relevant to Safety and Effectiveness

In §§ 315.3 and 601.32, FDA proposes to incorporate in its regulations the requirement in section 122 of FDAMA that the agency consider certain factors in determining the safety and effectiveness of diagnostic radiopharmaceuticals under section 505 of the act or section 351 of the PHS Act. These factors are as follows: (1) The proposed use of a diagnostic radiopharmaceutical in the practice of medicine; (2) the pharmacological and toxicological activity of a diagnostic radiopharmaceutical, including any carrier or ligand component; and (3) the estimated absorbed radiation dose of the diagnostic radiopharmaceutical. Other sections of the proposed regulations describe how the agency will assess these factors. In addition, FDA intends to provide further information in guidance to industry.

D. Indications

In §§ 315.4(a) and 601.33(a), FDA proposes to specify some of the types of indications for which the agency may approve a diagnostic radiopharmaceutical. These categories of indications are as follows: (1) Structure delineation; (2) functional, physiological, or biochemical assessment; (3) disease or pathology detection or assessment; and (4) diagnostic or therapeutic management. Approval may be possible for claims other than those listed. (In these and other provisions on diagnostic radiopharmaceuticals in the proposed rule, the terms "indication," "indication for use," and "claim" have the same meaning and are used interchangeably.)

A diagnostic radiopharmaceutical that is intended to provide structural delineation is designed to locate and outline anatomic structures. For

example, a radiopharmaceutical might be developed to distinguish a structure that cannot routinely be seen by any other imaging modality, such as a drug designed to image the lymphatics of the small bowel.

A diagnostic radiopharmaceutical that is intended to provide a functional, physiological, or biochemical assessment is used to evaluate the function, physiology, or biochemistry of a tissue, organ system, or body region. Functional, physiological, and biochemical assessments are designed to determine if a measured parameter is normal or abnormal. Examples of a functional or physiological assessment include the determination of the cardiac ejection fraction, myocardial wall motion, and cerebral blood flow. Examples of a biochemical assessment include the evaluation of sugar, lipid, protein, or nucleic acid synthesis or metabolism.

A diagnostic radiopharmaceutical that is intended to provide disease or pathology detection or assessment information assists in the detection, location, or characterization of a specific disease or pathological state. Examples of this type of diagnostic radiopharmaceutical include a radiolabeled monoclonal antibody used to attach to a specific tumor antigen and thus detect a tumor and a peptide that participates in an identifiable transporter function associated with a specific neurological disease.

A diagnostic radiopharmaceutical that is intended to assist in diagnostic or therapeutic patient management provides imaging, or related, information leading directly to a diagnostic or therapeutic patient management decision. Examples of this type of indication include: (1) Assisting in a determination of whether a patient should undergo a diagnostic coronary angiography or will have predictable clinical benefit from a coronary revascularization, and (2) assisting in a determination of the resectability of a primary tumor.

Proposed §§ 315.4(b) and 601.33(b) reflect the intent of section 122(a)(2) of FDAMA, which states that in appropriate cases, FDA may approve a diagnostic radiopharmaceutical for an indication that refers to "manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states." Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a process or to more than one disease or condition. This would allow FDA to approve a product

for an indication (e.g., delineation of a particular anatomic structure or functional assessment of a specific organ system) that would encompass manifestations of disease that are common to multiple disease states. An example of a manifestation that is common to multiple diseases is tumor metastases to the liver caused by various malignancies.

E. Evaluation of Effectiveness

The specific criteria that FDA would use to evaluate the effectiveness of a diagnostic radiopharmaceutical are stated in proposed §§ 315.5(a) and 601.34(a). These provisions state that FDA assesses the effectiveness of a diagnostic radiopharmaceutical by evaluating its ability to provide useful clinical information that is related to its proposed indication for use. The nature of the indication determines the method of evaluation, and because an application may include more than one type of claim, FDA might need to employ multiple evaluation criteria. FDA would require that any such claim be supported with information demonstrating that the potential benefit of the diagnostic radiopharmaceutical outweighs the risk to the patient from administration of the product.

Under proposed §§ 315.5(a)(1) and 601.34(a)(1), a claim of structure delineation would be established by demonstrating the ability of a diagnostic radiopharmaceutical to locate and characterize normal anatomic structures. In §§ 315.5(a)(2) and 601.34(a)(2), FDA proposes that a claim of functional, physiological, or biochemical assessment would be established by demonstrating that the diagnostic radiopharmaceutical could reliably measure the function or the physiological, biochemical, or molecular process. A reliable measurement would need to be supported by studies in normal and abnormal patient populations, consistent with the proposed claim and would require a qualitative or quantitative understanding of how the measurement varies in normal and abnormal subjects.

The agency proposes, in §§ 315.5(a)(3) and 601.34(a)(3), that a claim of disease or pathology detection or assessment would be established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical had sufficient accuracy in identifying or characterizing the disease or pathology. The term "accuracy" refers to the diagnostic performance of the product as measured by factors such as sensitivity, specificity, positive predictive value, negative predictive

value, and reproducibility of test interpretation. The term "sufficient accuracy" means accuracy that is good enough to indicate that the product would be useful in one or more clinical settings. FDA believes that the data demonstrating accuracy must be obtained from patients in a clinical setting(s) reflecting the proposed indication(s). For example, if a claim is for diagnosis of tumor in patients with a negative computed tomography (CT) scan for disease and a borderline serum carcinoembryonic antigen (CEA), the accuracy of the diagnostic radiopharmaceutical should be assessed in such patients rather than only in patients with CT-diagnosed disease or high serum CEA.

Under proposed §§ 315.5(a)(4) and 601.34(a)(4), for a claim of diagnostic or therapeutic patient management, the applicant must establish effectiveness by demonstrating in a defined clinical setting that the test is useful in such patient management. For example, an imaging agent might be studied in a manner that would demonstrate its usefulness in directing local excision of cancer-laden lymph nodes and sparing a wide area of nondiseased lymphatic tissue.

In §§ 315.5(a)(5) and 601.34(a)(5), FDA proposes that, for claims that do not fall within the indication categories in §§ 315.4 and 601.33, the applicant may consult with the agency on how to establish effectiveness.

Proposed §§ 315.5(b) and 601.34(b) specify that the accuracy and usefulness of diagnostic information provided by a diagnostic radiopharmaceutical must be determined by comparison with a reliable assessment of actual clinical status. To obtain such a reliable assessment, a diagnostic standard or standards of demonstrated accuracy must be used, if available. An example of such a standard is a tissue biopsy confirmation of a site of a diagnostic radiopharmaceutical localization. If an accurate diagnostic standard is not available, the actual clinical status must be established in some other manner, such as through patient followup.

FDA intends to develop a guidance document that will provide more detailed guidance to industry on the types of clinical investigations that would meet regulatory requirements for obtaining approval for particular types of indications for diagnostic radiopharmaceuticals. The guidance may address such matters as appropriate clinical endpoints and suitable diagnostic standards. For indications that are common to multiple disease states, the guidance may address clinical trial design and statistical

analysis considerations for patient populations that provide a range of representative disease processes.

F. Evaluation of Safety

FDA's proposed approach to the evaluation of the safety of diagnostic radiopharmaceuticals is set forth in §§ 315.6 and 601.35. Proposed §§ 315.6(a) and 601.35(a) state that the safety assessment of a diagnostic radiopharmaceutical includes, among other things, the following: The radiation dose; the pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand; the risks of an incorrect diagnostic determination; the adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

In §§ 315.6(b) and 601.35(b), FDA proposes that the assessment of the adverse reaction profile of a diagnostic radiopharmaceutical (including the carrier or ligand) include, but not be limited to, an evaluation of the product's potential to elicit the following: (1) Allergic or hypersensitivity responses, (2) immunologic responses, (3) changes in the physiologic or biochemical function of target and non-target tissues, and (4) clinically detectable signs or symptoms.

Proposed §§ 315.6(c)(1) and 601.35(c)(1) state that FDA may require, among other information, the following types of preclinical and clinical data to establish the safety of a diagnostic radiopharmaceutical: (1) Pharmacology data, (2) toxicology data, (3) a clinical safety profile, and (4) a radiation safety assessment. Other information that may be required to establish safety includes information on chemistry, manufacturing, and controls.

Under proposed §§ 315.6(c)(2) and 601.35(c)(2), the amount of new safety data required would depend on the characteristics of the diagnostic radiopharmaceutical and available information on the safety of the product obtained from other studies and uses. This information might include, but would not be limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide of the product, and results of preclinical studies on the product. Proposed §§ 315.6(c)(2) and 601.35(c)(2) further states that FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics that relate to safety risk and will specify the amount and type of safety data appropriate for each category. The paragraph states, as an example, that required safety data would be limited for diagnostic

radiopharmaceuticals with well-established low-risk profiles.

Proposed §§ 315.6(d) and 601.35(d) discusses the radiation safety assessment that will be required for a diagnostic radiopharmaceutical. FDA proposes that the applicant for approval of a diagnostic radiopharmaceutical establish the radiation dose of the product by radiation dosimetry evaluations in humans and appropriate animal models. Such evaluations must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. FDA notes that the use of occupational radiation dosimetry limits is not required in performing such evaluations. The maximum tolerated dose of the diagnostic radiopharmaceutical need not be established.

FDA intends to provide guidance on safety assessments for diagnostic radiopharmaceuticals. Such guidance may include a classification of diagnostic radiopharmaceuticals based on quantity administered, adverse event profile, and proposed patient population. The guidance would allow the safety information required to meet regulatory requirements to vary according to the class of the radiopharmaceutical. The guidance will also address evaluations of radiation dosimetry.

III. Analysis of Economic Impacts

FDA has examined the impact of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601-612), and under the Unfunded Mandates Reform Act (Pub. L. 104-114). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages, distributive impacts and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze significant regulatory options that would minimize any significant economic impact of a rule on small entities. The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any mandate that results in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any 1 year.

The agency has reviewed this proposed rule and has determined that

the rule is consistent with the principles set forth in the Executive Order and in these two statutes. FDA finds that the rule will not be a significant rule under the Executive Order. Further, the agency finds that, under the Regulatory Flexibility Act, the rule will not have a significant economic impact on a substantial number of small entities. Also, since the expenditures resulting from the standards identified in the rule are less than \$100 million, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

The proposed rule clarifies existing FDA requirements for the approval and evaluation of drug and biological products already in place under the act and the PHS Act. Existing regulations (parts 314 and 601) specify the type of information that manufacturers are required to submit in order for the agency to properly evaluate the safety and effectiveness of new drugs or biological products. Such information is usually submitted as part of a new drug application (NDA) or biological license application or as a supplement to an approved application. The information typically includes both nonclinical and clinical data concerning the product's pharmacology, toxicology, adverse events, radiation safety assessments, chemistry, and manufacturing and controls.

The proposed regulation recognizes the unique characteristics of diagnostic radiopharmaceuticals and sets out the agency's approach to the evaluation of these products. For certain diagnostic radiopharmaceuticals, the proposed regulation may reduce the amount of safety information that must be obtained by conducting new clinical studies. This would include approved radiopharmaceuticals with well-established low-risk safety profiles because such products might be able to use scientifically sound data established during use of the radiopharmaceutical to support the approval of a new indication for use. In addition, the clarification achieved by the proposed rule is expected to reduce the costs of submitting an application for approval of a diagnostic radiopharmaceutical by improving communications between applicants and the agency and by reducing wasted effort directed toward the submission of data that is not necessary to meet the statutory approval standard.

Manufacturers of in vitro and in vivo diagnostic substances are defined by the Small Business Administration as small businesses if such manufacturers employ fewer than 500 employees. The agency finds that only 2 of the 8

companies that currently manufacture or market radiopharmaceuticals have fewer than 500 employees.¹ Moreover, the proposed rule would not impose any additional costs but, rather, is expected to reduce costs for manufacturers of certain diagnostic radiopharmaceuticals, as discussed previously. Therefore, in accordance with the Regulatory Flexibility Act, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

IV. Proposed Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 30 days after the date of its publication in the **Federal Register**.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). A description of these provisions is shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

¹ Medical and Healthcare Marketplace Guide, Dorland's Biomedical, sponsored by Smith Barney Health Care Group, 13th ed., 1997 to 1998.

Title: Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring.

Description: FDA is proposing regulations for the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring. The proposed rule would clarify existing FDA requirements for approval and evaluation of drug and biological products already in place under the authorities of the act and the PHS Act. Those regulations, which appear in primarily at parts 314 and 601, specify the information that manufacturers must submit to FDA for the agency to properly evaluate the safety and effectiveness of new drugs or biological products. The information, which is usually submitted as part of an NDA or new biological license application or as a supplement to an approved application, typically includes, but is not limited to, nonclinical and clinical data on the pharmacology, toxicology, adverse events, radiation safety assessments, and chemistry, manufacturing and controls. The content and format of an application for approval of new drugs and antibiotics are set out in § 314.50 and for new biological products in § 601.25. Under the proposed regulation, information required under the act and the PHS Act

and needed by FDA to evaluate safety and effectiveness would still need to be reported.

Description of Respondents: Manufacturers of in vivo radiopharmaceuticals used for diagnosis and monitoring.

To estimate the potential number of respondents that would submit applications or supplements for diagnostic radiopharmaceuticals, FDA used the number of approvals granted in fiscal year 1997 (FY 1997) to approximate the number of future annual applications. In FY 1997, FDA approved seven diagnostic radiopharmaceuticals and received one new indication supplement; of these, three respondents received approval through the Center for Drug Evaluation and Research and five received approval through the Center for Biologics Evaluation and Research. The annual frequency of responses was estimated to be one response per application or supplement. The hours per response refers to the estimated number of hours that an applicant would spend preparing the information referred to in the proposed regulations. The time needed to prepare a complete application is estimated to be approximately 10,000 hours, roughly one-fifth of which, or 2,000 hours, is estimated to be spent preparing the

portions of the application that are affected by these proposed regulations. The proposed rule would not impose any additional reporting burden beyond the estimated current burden of 2,000 hours because safety and effectiveness information is already required by preexisting regulations (parts 314 and 601). In fact, clarification by the proposed regulation of FDA's standards for evaluation of diagnostic radiopharmaceuticals is expected to streamline overall information collection burdens, particularly for diagnostic radiopharmaceuticals that may have well-established low-risk safety profiles, by enabling manufacturers to tailor information submissions and avoid conducting unnecessary clinical studies. The following table indicates estimates of the annual reporting burdens for the preparation of the safety and effectiveness sections of an application that are imposed by existing regulations. The burden totals do not include an increase in burden because no increase is anticipated. This estimate does not include the actual time needed to conduct studies and trials or other research from which the reported information is obtained. FDA invites comments on this analysis of information collection burdens.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
315.4, 315.5, and 315.6	3	1	3	2,000	6,000
601.33, 601.34, and 601.35	5	1	5	2,000	10,000
Total	8		8		16,000

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Interested persons and organizations may submit comments on the information collection requirements of this proposed rule by June 22, 1998, to Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

At the close of the 30-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of the proposed rule, FDA will publish a notice in the **Federal Register** of OMB's

decision to approve, modify, or disapprove the information collection provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VII. Request for Comments

Interested persons may, on or before August 5, 1998, submit to the Dockets Management Branch (address above) written comments on this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 315

Biologics, Diagnostic radiopharmaceuticals, Drugs.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, the Food and Drug Modernization Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR chapter I be amended as follows:

1. Part 315 is added to read as follows:

PART 315—DIAGNOSTIC RADIOPHARMACEUTICALS

Sec.

- 315.1 Scope.
315.2 Definition.
315.3 General factors relevant to safety and effectiveness.
315.4 Indications.
315.5 Evaluation of effectiveness.
315.6 Evaluation of safety.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e; sec. 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 315.1 Scope.

The regulations in this part apply to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. They do not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical shall be evaluated taking into account each intended use.

§ 315.2 Definition.

For purposes of this part, diagnostic radiopharmaceutical means:

- (a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or
- (b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§ 315.3 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical shall include consideration of the following:

- (a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;
- (b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and
- (c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§ 315.4 Indications.

- (a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:
- (1) Structure delineation.
- (2) Functional, physiological, or biochemical assessment.

(3) Disease or pathology detection or assessment.

(4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a process or to more than one disease or condition.

§ 315.5 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation will vary depending upon the proposed indication(s) and may use one or more of the following criteria:

- (1) The claim of structure delineation is established by demonstrating the ability to locate and characterize normal anatomical structures.
- (2) The claim of functional, physiological, or biochemical assessment is established by demonstrating reliable measurement of function(s) or physiological, biochemical, or molecular process(es).
- (3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.
- (4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in § 315.4, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

(b) The accuracy and usefulness of the diagnostic information shall be determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status shall be established in another manner, e.g., patient followup.

§ 315.6 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following: The radiation

dose; the pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand; the risks of an incorrect diagnostic determination; the adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

- (1) Allergic or hypersensitivity responses.
- (2) Immunologic responses.
- (3) Changes in the physiologic or biochemical function of the target and non-target tissues.
- (4) Clinically detectable signs or symptoms.
- (c) (1) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:
- (i) Pharmacology data.
- (ii) Toxicology data.
- (iii) Clinical adverse event data.
- (iv) Radiation safety assessment.

(2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical obtained from other studies and uses. Such information may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of preclinical studies. FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data appropriate for each category. For example, for a category of radiopharmaceuticals with a well-established low-risk profile, required safety data will be limited.

(d) The radiation safety assessment shall establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. The maximum tolerated dose need not be established.

PART 601—LICENSING

2. The authority citation for part 601 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374,

379e, 381; 42 U.S.C. 216, 241, 262, 263; 15 U.S.C. 1451-1461; sec. 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.33 [Redesignated as § 601.28]

3. Section 601.33 *Samples for each importation* is redesignated as § 601.28 and transferred from subpart D to subpart C, and the redesignated section heading is revised to read as follows:

§ 601.28 Foreign establishments and products: samples for each importation.

* * * * *

4. Subpart D is amended by revising the title and adding §§ 601.30 through 601.35 to read as follows:

Subpart D—Diagnostic Radiopharmaceuticals

Sec.

601.30 Scope.
601.31 Definition.
601.32 General factors relevant to safety and effectiveness.
601.33 Indications.
601.34 Evaluation of effectiveness.
601.35 Evaluation of safety.

Subpart D—Diagnostic Radiopharmaceuticals

§ 601.30 Scope.

This subpart applies to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. It does not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical shall be evaluated taking into account each intended use.

§ 601.31 Definition.

For purposes of this subpart, diagnostic radiopharmaceutical means:

- (a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or
- (b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§ 601.32 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical shall include consideration of the following:

- (a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;

- (b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and

- (c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§ 601.33 Indications.

(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:

- (1) Structure delineation.
- (2) Functional, physiological, or biochemical assessment.
- (3) Disease or pathology detection or assessment.
- (4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a process or to more than one disease or condition.

§ 601.34 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation will vary depending upon the proposed indication and may use one or more of the following criteria:

- (1) The claim of structure delineation is established by demonstrating the ability to locate and characterize normal anatomical structures.
- (2) The claim of functional, physiological, or biochemical assessment is established by demonstrating reliable measurement of function(s) or physiological, biochemical, or molecular process(es).
- (3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.
- (4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in § 601.33, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

- (b) The accuracy and usefulness of the diagnostic information shall be

determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status shall be established in another manner, e.g., patient followup.

§ 601.35 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following: The radiation dose; the pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand; the risks of an incorrect diagnostic determination; the adverse reaction profile of the drug; and results of human experience with the radiopharmaceutical for other uses.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

- (1) Allergic or hypersensitivity responses.
- (2) Immunologic responses.
- (3) Changes in the physiologic or biochemical function of the target and non-target tissues.
- (4) Clinically detectable signs or symptoms.

(c) (1) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:

- (i) Pharmacology data.
 - (ii) Toxicology data.
 - (iii) Clinical adverse event data.
 - (iv) Radiation safety assessment.
- (2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical obtained from other studies and uses. Such information may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of preclinical studies. FDA will categorize diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data appropriate for each category. For example, for a category of radiopharmaceuticals with a well-established low-risk profile, required safety data will be limited.

(d) The radiation safety assessment shall establish the radiation dose of a

diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation must consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. The maximum tolerated dose need not be established.

Dated: April 15, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98-13797 Filed 5-20-98; 11:44 am]

BILLING CODE 4160-01-F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 89

[FRL-6014-4]

RIN 2060-AH65

Control of Emissions of Air Pollution from New CI Marine Engines at or Above 37 Kilowatts

AGENCY: Environmental Protection Agency (EPA).

ACTION: Advance notice of proposed rulemaking.

SUMMARY: EPA is issuing this Advance Notice of Proposed Rulemaking (ANPRM) to invite comment from all interested parties on EPA's plans to propose emission standards and other related provisions for new propulsion and auxiliary marine compression-ignition (CI) engines at or above 37 kilowatts (kW). This action supplements an earlier action for these engines initiated as part of an overall control strategy for new spark-ignition (SI) and CI marine engines (Notice of Proposed Rulemaking (NPRM) published November 9, 1994, modified in a Supplemental Notice of Proposed Rulemaking (SNPRM) published at February 7, 1996). The engines covered by today's action are used for propulsion and auxiliary power on both commercial and recreational vessels for a wide variety of applications including, but not limited to, barges, tugs, fishing vessels, ferries, runabouts, and cabin cruisers. This document does not address diesel marine engines rated under 37 kW, which are included in a proposed rulemaking for land-based nonroad CI engines published at September 24, 1997.

DATES: EPA requests comment on this ANPRM no later than June 22, 1998. Should a commenter miss the requested deadline, EPA will try to consider any comments received prior to publication

of the NPRM that is expected to follow this ANPRM. There will also be opportunity for oral and written comment when EPA publishes the NPRM.

ADDRESSES: Materials relevant to this action are contained in Public Docket A-97-50, located at room M-1500, Waterside Mall (ground floor), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. The docket may be inspected from 8:00 a.m. until 5:30 p.m., Monday through Friday. A reasonable fee may be charged by EPA for copying docket materials.

Comments on this notice should be sent to Public Docket A-97-50 at the above address. EPA requests that a copy of comments also be sent to Jean Marie Revelt, U.S. EPA, 2565 Plymouth Road, Ann Arbor, MI 48105.

FOR FURTHER INFORMATION CONTACT: Margaret Borushko, U.S. EPA, Engine Programs and Compliance Division, (734) 214-4334.

SUPPLEMENTARY INFORMATION:

I. Purpose and Background

A. Purpose

Ground level ozone levels continue to be a significant problem in many areas of the United States. In the past, the main strategy employed in efforts to reduce ground-level ozone was reduction of volatile organic compounds (VOCs). In recent years, however, it has become clear that NO_x controls are often a more effective strategy for reducing ozone. As a result, attention has turned to NO_x emission controls as the key to improving air quality in many areas of the country. Building on the emission standards for CI engines promulgated in the early 1990s, EPA has recently promulgated a new emission control program for on-highway CI engines and proposed a new program for nonroad CI engines.^{1, 2} Both of these programs contain stringent standards that will greatly reduce NO_x emissions from these engines.

Similarly, particulate matter (PM) is also a problem in many areas of the country. Currently, there are 80 PM-10 nonattainment areas across the U.S. (PM-10 refers to particles less than or equal to 10 microns in diameter). PM, like ozone, has been linked to a range of serious respiratory health problems. Levels of PM caused by mobile sources are expected to rise in the future, due to the predicted increase in the number of

¹ In this notice, the term "land-based nonroad" and "nonroad" refers to the land-based CI engines and equipment regulated under 40 CFR part 89. It does not include locomotive engines.

² See 62 FR 54694 (October 21, 1997) and 62 FR 50152 (September 24, 1997).

individual mobile sources. Both of the new emission programs referred to above, for on-highway and nonroad CI engines, are anticipated to reduce ambient PM levels, either through a reduction in directly emitted particulate matter or through a reduction in indirect (atmospheric) PM formation caused by NO_x emissions.

Domestic and ocean-going CI marine engines account for approximately 4.5 percent of total mobile source NO_x emissions nationwide. However, because of the nature of their operation, the contribution of these engines to NO_x levels in certain port cities and coastal areas is much higher. To address these emissions, today's action outlines a control program for CI marine engines at or above 37 kW that builds on EPA's programs for on-highway and land-based nonroad diesel engines identified above, EPA's recent locomotive rule, discussed below, and the International Convention on the Prevention of Pollution from Ships (MARPOL 73/78), Annex VI—Air Pollution developed by the International Maritime Organization (IMO).³ If the emission standards and other requirements for those CI marine engines that use the same technologies reflected in EPA's on-highway, land-based nonroad, or locomotive rules are implemented as discussed in today's action, EPA would expect to see NO_x and PM reductions on a per-engine basis comparable to those achieved by engines subject to those rules. The numerical levels that EPA is considering applying to very large CI marine engines were intended by IMO to result in a 30 percent NO_x reduction. EPA continues to investigate IMO's anticipated reductions for those engines, based on the age and other characteristics of the U.S. fleet.

B. Statutory Authority

Section 213(a) of the Clean Air Act (CAA) directs EPA to: (1) conduct a study of emissions from nonroad engines and vehicles; (2) determine whether emissions of carbon monoxide (CO), oxides of nitrogen (NO_x), and volatile organic compounds (VOCs, including hydrocarbons (HC)) from nonroad engines and vehicles are significant contributors to ozone or CO in more than one area which has failed to attain the national ambient air quality standards (NAAQS) for ozone or CO; and (3) if nonroad emissions are determined to be significant, regulate those categories or classes of new

³ A copy of MARPOL 73/78 Annex VI and the associated NO_x Technical Code is available in this docket.

Assessment of Coronary Artery Disease Severity by Positron Emission Tomography

Comparison With Quantitative Arteriography in 193 Patients

Linda L. Demer, MD, PhD, K. Lance Gould, MD, Richard A. Goldstein, MD,
Richard L. Kirkeeide, PhD, Nizar A. Mullani, Richard W. Smalling, MD, PhD,
Akira Nishikawa, MD, and Michael E. Merhige, MD

With the technical assistance of Mary Haynie, RN, and Richard L. Holmes, RT

To assess the accuracy of positron emission tomography (PET) for evaluation of coronary artery disease (CAD), cardiac PET perfusion images were obtained at rest and with dipyridamole-handgrip stress in 193 patients undergoing coronary arteriography. PET images were reviewed by two independent readers blinded to clinical data. Subjective defect severity scores were assigned to each myocardial region on a 0 (normal) to 5 (severe) scale. Results were compared with arteriographic stenosis severity expressed as stenosis flow reserve (SFR), with continuous values ranging from 0 (total occlusion) to 5 (normal), calculated from quantitative arteriographic dimensions using automated detection of the vessel borders. There were 115 patients with significant CAD ($SFR < 3$), 37 patients with mild CAD ($3 \leq SFR < 4$), and 41 patients with essentially normal coronaries ($SFR \geq 4$). With increasingly severe impairment of stenosis flow reserve, subjective PET defect severity increased. Despite wide scatter, a PET score of 2 or more was highly predictive of significant flow reserve impairment ($SFR < 3$). For each patient, the score of the most severe PET defect correlated with the SFR of that patient's most severe stenosis ($r_s = 0.77 \pm 0.06$). For each of 243 stenoses, PET defect score correlated with the SFR of the corresponding artery ($r_s = 0.63 \pm 0.08$). PET defect location closely matched the region supplied by the diseased artery, and readers agreed whether the most severe PET defect was less than or more than 2 for 89% of patients. (*Circulation* 1989;79:825-835)

Myocardial perfusion imaging is widely used for noninvasive assessment of stenosis severity. Knowledge of the diagnostic accuracy of these tests is important for proper clinical application and interpretation. Most previous reports of the diagnostic accuracy of myocardial perfusion imaging¹⁻⁴ have used sensitivity-

specificity analysis to describe the relation between image defects and arteriographic disease. This method requires binary (positive or negative) classification of both imaging and arteriographic results. Arteriographic results have usually been described in terms of percent diameter narrowing, with a threshold value of 50% as the criterion for presence of coronary disease.

There are three limitations to this use of sensitivity-specificity analysis for assessing accuracy of noninvasive tests for coronary disease. First, coronary disease is not an all-or-none condition; binary classification requires arbitrary threshold criteria and creates artificial distinctions in coronary artery disease that, in actuality, has a continuous spectrum of severity.

Threshold values that yield optimal sensitivity and specificity values for one test may yield falsely lower values for a different but more accurate test if its detection threshold is different. For example, an imaging test capable of detecting 40% stenoses may have low specificity according to a 50% stenosis

From the Division of Cardiology, Department of Medicine, and Positron Diagnostic and Research Center, University of Texas Medical School, Houston, Texas.

Presented in part as an abstract at the American College of Cardiology Scientific Session, March 28, 1988.

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Address for correspondence: Linda L. Demer, MD, PhD, Division of Cardiology, UCLA School of Medicine, 47-123 CHS, 10833 LeConte Avenue, Los Angeles, CA 90024-1679.

Address for reprints: K. Lance Gould, MD, Division of Cardiology, University of Texas Medical School, P.O. Box 20708, Houston, TX 77225.

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criterion but high specificity according a 40% stenosis criterion.

Second, sensitivity and specificity values are also determined by the disease distribution of the study population.⁵ A sample population with a high frequency of mild disease will be distributed centrally near the threshold values where scatter is more likely to lower sensitivity and specificity. The sensitivity and specificity found in one population may not apply to a different population. To overcome these limitations, analysis of test results as continuous variables has been proposed.⁶

Finally, recent reports by Marcus and others^{7,8} have indicated that percent diameter narrowing is not an adequate standard for quantifying stenosis severity in clinical studies. It does not account for the effects of diffuse disease, inherent eccentricity, stenosis length, viscosity, cross-sectional area, entrance and exit angles, and absolute dimensions on flow impedance; and it is limited by substantial interobserver and intraobserver variability.⁹⁻¹¹ Proposed alternative approaches include quantitative arteriographic methods based on the Brown-Dodge method¹² to calculate stenosis flow reserve¹³ and direct measurement of coronary flow velocity by Doppler catheter.¹⁴

In an earlier study, Wijns and colleagues¹⁵ used quantitative arteriographic and direct physiologic measurements to assess the accuracy of planar ²⁰¹Tl imaging, but they retained the conventional threshold criteria to classify arteriographic severity and perfusion defect severity as positive or negative. The feasibility of clinical PET perfusion imaging has also been addressed in previous work by Schelbert and colleagues¹⁶ and, with quantitative arteriographic flow reserve, by our group.¹⁷ These studies also retained the binary classification system and involved small numbers of patients.

The purpose of the present study was to reevaluate the accuracy of positron perfusion imaging in assessment of coronary disease severity with scales covering the range of disease severity rather than binary classification, direct correlation rather than sensitivity-specificity analysis, and quantitative arteriographic flow reserve rather than percent diameter narrowing, in a large series of patients.

Methods

Study Patients

Subjects consisted of 193 patients (143 men, 50 women) undergoing diagnostic cardiac catheterization. The patient sample included 50 patients previously reported in a study where binary classification and sensitivity-specificity analysis were used.¹⁷ Clinical indications for arteriography included chest pain syndromes, myocardial infarction, abnormal stress tests, coronary angioplasty, thrombolytic therapy for acute infarction, evaluation before renal transplant, before and after cholesterol lowering programs, or as part of screening feasibility studies.

Sixty-six patients were clinically diagnosed as having a previous myocardial infarction. From an initial group of 209 patients, 12 early patients were excluded because part of the heart was not imaged due to positioning error, and four PET images were not interpretable due to camera or computer malfunction. Patients were not enrolled if there was evidence of unstable angina or active bronchospasm with theophylline bronchodilator therapy, which are contraindications to intravenous dipyridamole. After informed consent was obtained, coronary arteriography and PET imaging were performed according to protocols approved by the University of Texas Committee for Protection of Human Subjects.

Quantitative Arteriography

Cineangiographic frames of orthogonal views were digitized for each stenosis involving a major artery, including diagonal, obtuse marginal, ramus intermedius, and acute marginal branches. Absolute and relative stenosis dimensions were measured with a computer program providing automatic detection of vessel borders (Figure 1), with an accuracy of ± 0.1 mm. The theory and equations for predicting stenosis flow reserve from these dimensions have been described previously.^{13,18} In brief, the coronary perfusion pressure distal to each stenosis was calculated as a function of flow^{19,20} according to the equation:

$$P_{cor} = P_{Ao} - (fQ + sQ^2)$$

where P_{cor} is distal coronary pressure, P_{Ao} is aortic pressure, Q is flow, f is $8\mu\pi L/A_s^2$, s is $\rho((1/A_s) - (1/A_n))^2$, A_s is minimum absolute area, A_n is absolute area of normal adjacent artery, μ is blood viscosity, ρ is blood density, and L is stenosis length.

This relation, shown as the curved line in Figure 1, lower panel, was compared with the known pressure-flow relation for conditions of maximal coronary vasodilation, shown as the diagonal line. Stenosis flow reserve (SFR) was defined as the intersection of these two relations (i.e., flow at maximum coronary vasodilation) relative to rest flow, under standardized hemodynamic conditions. In comparison with direct measurements by electromagnetic flow meter, the 95% confidence interval was ± 0.66 with a reproducibility of 2-3%.¹³ The advantages of SFR over other methods of describing stenosis severity have been discussed in detail in a recent editorial.²¹

Coronary arteries were considered normal if patent bypass grafts supplied the arterial bed (two patients). Five patients having their PET study after acute myocardial infarction, with normal coronary arteriography after revascularization of chronic occlusions, were considered to have total occlusions for the purposes of patient-by-patient analysis. Infarct-related stenoses of 19 patients who had undergone acute revascularization were excluded from this analysis because the residual stenosis severity would not be comparable to the variable degree of resultant perfusion defect; the remaining stenoses in these patients were included in the regional analysis.

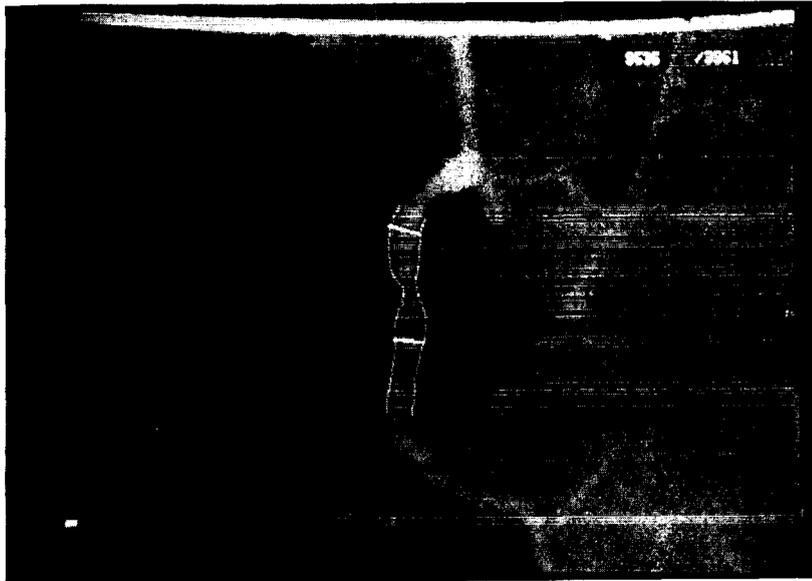


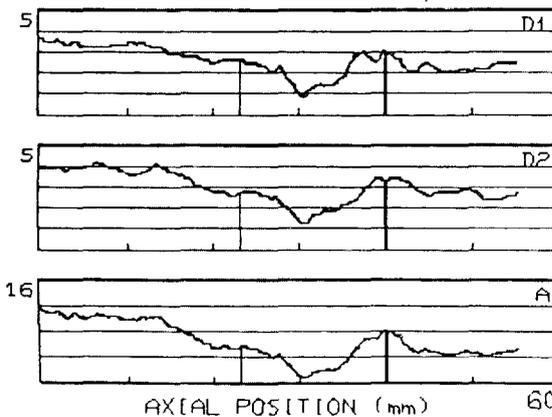
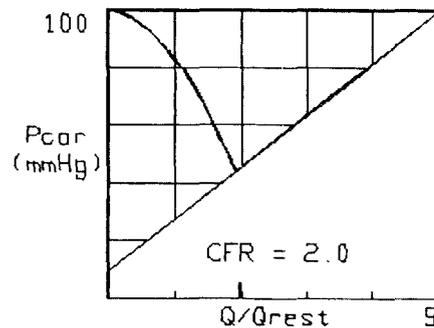
FIGURE 1. Top panel: Automated edge-detection analysis of a coronary arteriogram. Bottom panel: Quantitative arteriographic data for another patient including plots of diameter and cross-sectional lumen area as functions of axial position (lower left); parameters calculated from dimensions including minimal, proximal, distal, and percent diameter in each view (D_1, D_2), minimal, proximal, distal, and percent cross-sectional area, volume, length, and relative length of the stenosed segment, entrance and exit angles (α and Ω), predicted rest flow (Q_r), and viscous and expansion loss coefficients (C_v, C_e, K_v, K_e) (upper left); and the derived pressure-flow relation and stenosis flow reserve (upper right). The diagonal line crossing the pressure-flow curve represents the condition of maximal arteriolar vasodilation. As flow increases, pressure distal to the stenosis decreases, until it reaches a minimum at the point of maximal vasodilation. Stenosis flow reserve is defined as that maximum value of flow relative to resting flow (Q/Q_r) under standardized hemodynamic conditions, where normal stenosis flow reserve is 5.

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Quantitative Arteriography
UTHSCH/Cardiology

1-SEP-88
ART002177

	Prox	Min	Dist	%Red	Norm
D1(mm)	2.65	0.87	3.02	71	3.02
D2(mm)	2.79	1.29	3.33	61	3.33
A(mm ²)	5.80	0.89	7.91	89	7.91
L(mm)	17.0	L/Dn	5.4	U(mm ³)	69.8
Alpha	-19.8	Omeg	13.7		
An(mm ²)	7.9	Kv	2053	Ke	1.40
Qr(cc/s)	1.6	Cv	2.15	Ce	5.36



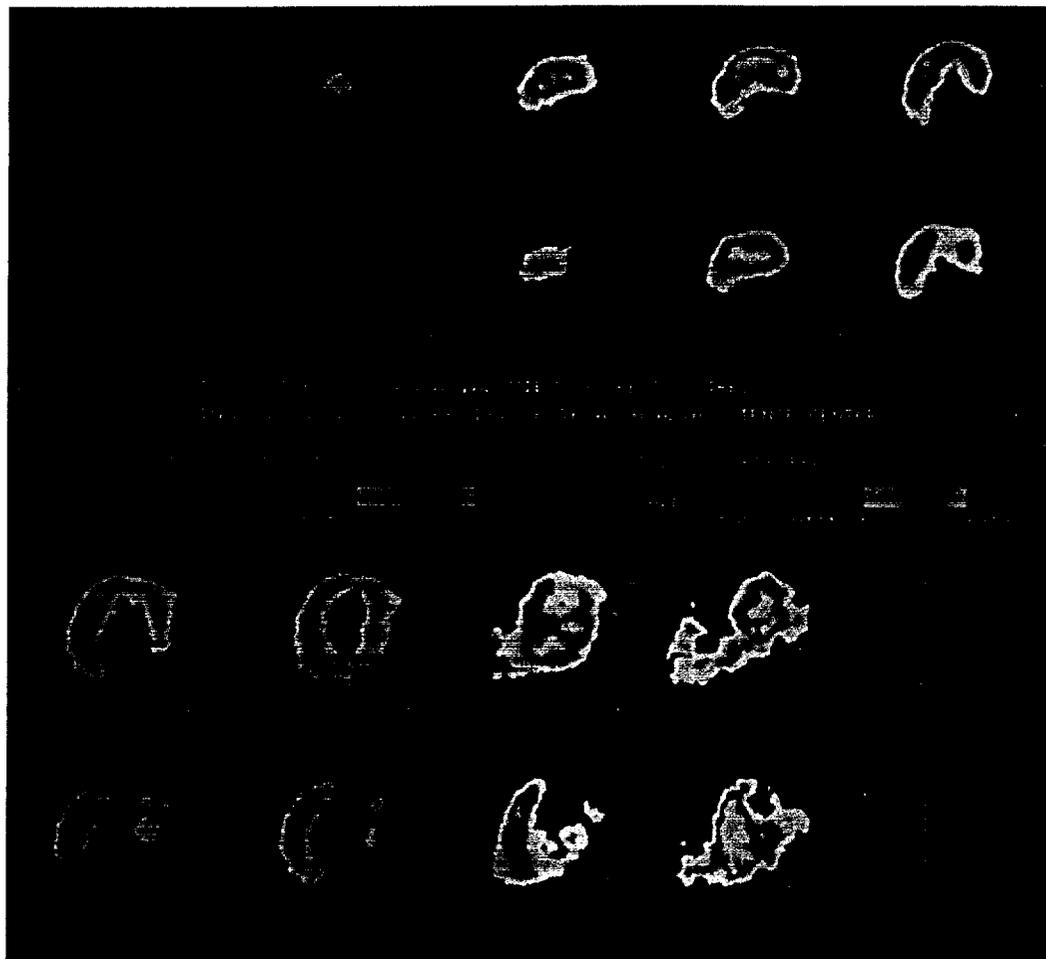


FIGURE 2. Positron emission tomographic ^{82}Rb images acquired from a patient with proximal disease of the left anterior descending artery before (top row of upper and lower images) and after (bottom row) intravenous dipyridamole with handgrip stress. The views are oriented in the oblique semi-long axis and arranged in vertical order from base (upper left) to inferior wall (lower right). Each slice is viewed from above so that the apex is at the top, the lateral free wall on the left, the valve ring at the bottom, and the interventricular septum at the upper right of the horseshoe-shaped left ventricular slices. In the color coding, white is the highest, red next highest, yellow intermediate, and green and blue lowest uptake. There is a large anterior, septal, and apical defect. The right ventricular wall is not normally visualized on PET imaging due to its thin walls.

Positron Emission Tomography

Patients were fasted for 4 hours, and caffeine and theophylline were withheld for 8 hours before imaging to prevent interference with the hyperemic effect of dipyridamole. Fluoroscopy was used to mark the cardiac borders for proper patient positioning. Scans were performed with the University of Texas multislice tomograph^{17,22} with a reconstructed resolution of 14 mm full-width half-maximum. Transmission images were performed to correct for photon attenuation. Emission images were obtained with ^{82}Rb produced by a portable generator²³ or, when ^{82}Rb was not available, ^{13}N ammonia.^{17,24,25} Eighty-two patients received ^{82}Rb and 111 received ^{13}N ammonia. The tracer was injected through a 20-gauge catheter inserted into an antecubital vein. To allow for blood pool clearance, there was a 1-minute delay after ^{82}Rb and a

3-minute delay after ammonia administration. After this delay, data were acquired for 5–8 minutes for ^{82}Rb and 15–20 minutes for ^{13}N ammonia. After isotope decay, 10 minutes after administration of the first dose of ^{82}Rb or 40 minutes after ^{13}N ammonia, dipyridamole (0.142 mg/kg/min) was infused for 4 minutes. Two minutes after the infusion was completed, 25% of the predetermined maximal handgrip was begun as described by Brown.²⁶

At 8 minutes from onset of the infusion, a second dose of the same amount of the same tracer was injected, and imaging was repeated. Data were acquired over the same period. Radiation doses involved in these procedures have been described previously.^{27–29} For those patients developing significant angina, aminophylline (125 mg) was given intravenously.

Image Interpretation

As previously described,¹⁷ rest and stress images with nine tomographic slices each, were displayed in an isocount color format. This format consisted of five primary colors (white, red, yellow, green, and blue) in order of highest to lowest counts, each divided into 3% gradations of shade. Images were visually interpreted by two independent readers (KLG, RAG) blinded to clinical data. In two cases, only one interpretation was available due to loss of data files. Rest and stress images were displayed either side-by-side or superimposed with adjustable color scales (Figure 2).

Seven regions of each cardiac image (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were evaluated. Perfusion defects, defined as regions of subjectively lower counts in at least two contiguous slices compared to the remainder of the heart, were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects, respectively. One score was assigned to each region. Each step of the scale corresponded to approximately one primary color step. For example, in general, a red region adjacent to a white region was not considered a definite defect; however, yellow adjacent to white was considered a definite defect. Relative size of the defect was also included in assigning the scale to allow for pixel noise. The average of the two readings was taken for each region, in effect resulting in an 11-point scale (0 through 5 in 0.5 increments) of PET defect severity.

Interobserver Differences in PET Scan Interpretation

PET defect scores assigned to each region by the two readers were compared for variability according to the criteria shown in Table 2. A similar method has been used to assess interobserver differences in interpretation of thallium perfusion images.²⁹ Due to overlap of some portions of the seven cardiac regions defined above, minor differences in the description of regions contiguous to a large defect were allowed. For example, if a defect were described by one reader as having a grade 4 defect in the anterior, apical, and anteroseptal regions and 0 in the anterolateral region, whereas the other reader assigned a score of 4 to all four regions, then the readings were considered in essential agreement despite the difference in scores for the anterolateral region.

In eight cases, the qualitative interpretations differed markedly, and the readings were repeated independently. On repeat reading, the interpretations remained in disagreement except in two cases. The new readings were used for these two patients. For the other six, a mean of the divergent scores was used, as for the remaining patients.

TABLE 1. Relation of PET Defect Location to Stenosed Coronary Artery in One-Vessel Disease

LAD-diagonal	
Anterior	11
Anterolateral-antroseptal	7
Anterior and inferior	2
Anteroseptal and posterolateral	2
None	
SFR > 3	13
SFR < 3	2
Circumflex	
Posterolateral	10
Posterior or lateral	4
Anterior	1
None	
SFR < 3	1
Right coronary	
Inferior	8
Inferolateral	2
Inferoapical-apical	6
Inferoseptal	2
Anterolateral	1
None	
SFR > 3	1
SFR < 3	2

LAD, left anterior descending coronary artery; SFR, stenosis flow reserve.

Comparison of PET defect location with site of coronary artery narrowing for patients with one-vessel disease with SFR < 4.

Analysis

To determine the relation of PET defect severity to stenosis flow reserve, two analyses were used. First, the PET defect score was compared with its presumed corresponding artery for each defect-stenosis pair. Only the most severe stenosis was considered for each artery, and patients with neither stenoses nor PET defects were counted as only a single data pair rather than three pairs to prevent overweighting the extreme normal end of the scale. The anterior, septal, and anterolateral regions were associated with the LAD; the posterolateral region was associated with the circumflex; and the inferoposterior region was associated with the right coronary artery. Diagonal and ramus intermedius branches were associated with the same region as the LAD.

Second, because it may be difficult to determine with absolute certainty which artery corresponds to a given region, the data were also analyzed by comparing the most severe PET defect with the most severe SFR for each patient. The nonparametric rank correlation coefficients, standard errors, and confidence intervals were determined by the Spearman method and reported as the Spearman correlation coefficient, r_s , \pm two times the SEE. Least-squares method was used to calculate the regression coefficients. Fisher's exact test was used to compare results of the two perfusion tracers.

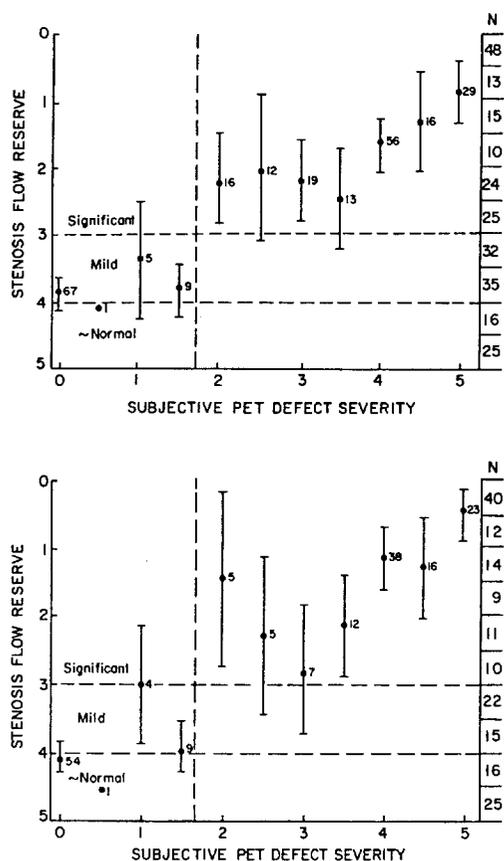


FIGURE 3. Top panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in the corresponding anatomic region for 243 stenoses. Mean value of SFR is plotted as a function of PET defect severity. The horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses. The error bars represent 90% confidence intervals. The number of patients represented is shown adjacent to each point. Right-hand column lists the numbers of patients found in each interval of SFR, to illustrate the distribution of coronary disease in this population. SFR is plotted on a reverse scale (5 to 0) to parallel stenosis severity. No error bars are shown for the point representing a single stenosis. Bottom panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in 174 patients. The most severe stenosis was compared with the most severe PET defect for each patient. Nineteen patients with revascularization during acute infarction were excluded because the residual stenosis severity would not be comparable to the severity of the fixed perfusion defect. As for the top panel, the horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses.

Results

Coronary Arteriography

Coronary artery stenoses with flow reserve values less than 4 were found in 137 patients. Thirty-seven of these patients had stenosis flow reserve values between 3 and 4, consistent with mild disease. Fifteen had myocardial infarction with revascularization. Occlusive disease was present in 34, involving 42 vessels.

PET Defect Severity Versus Stenosis Severity for Each Artery

For the 243 stenosis-defect pairs among the 193 patients, PET defect score was compared with arteriographic severity of the corresponding coronary stenosis (Figure 3, top). With increasing impairment of flow reserve, subjective PET defective severity increases. Although there is wide scatter, a PET defect score of 2 or more, indicated by the vertical line in Figure 3, top, is highly predictive of significant flow reserve impairment ($SFR < 3$). PET score rank correlated significantly with SFR ($r_s = 0.63 \pm 0.08$). Linear regression yielded the equation:

$$\text{predicted SFR} = 3.91 - 0.55 (\text{PET defect rank})$$

with standard errors for the coefficients of 1.4 and 0.04, respectively. This regression equation is provided for description rather than for calculations; because of the scatter in the relation, direct calculation of any individual value of SFR from PET defect score would not be accurate. Mean values are shown for clarity because of overlap of the large number of data points; regression was performed with the raw data. Although the correlation coefficient is negative, the slope is positive in Figure 3, top, because the vertical scale was reversed in the figure for convenience so that SFR would parallel stenosis severity.

PET Defects Compared With Arteriographic Severity for Each Patient

To determine whether PET defects identify patients with coronary disease, irrespective of location, the SFR of the most severe stenosis was compared to the score of the most severe PET defect for each patient over the entire range of disease severity (Figure 3, bottom).

As in the preceding figure, increasing impairment of flow reserve corresponds to increasing PET defect severity. Although there is wide scatter, a PET defect score of 2 or more (indicated by the vertical line in Figure 3, bottom) is predictive of significant flow impairment ($SFR < 3$). The SEMs are larger for the middle range of stenosis severity (from 2 to 4) than for the extremes. This is attributable in part to the smaller numbers of PET defects in this range. In addition, several of these defects correspond to lesions in diagonal arteries or in distal portions of the larger arteries, affecting small regions of myocardium. The severity of such small defects

TABLE 2. Interobserver Differences in PET Scores

Classification	Difference	Maximal score	
		Rest scans	Stress scans
Agreement			
Identical	0	75 (40%)	59 (31%)
Essential	1	66 (35%)	86 (45%)
Near	2	14 (7%)	14 (7%)
Disagreement			
Mild	3	19 (10%)	16 (8%)
Moderate	4	4 (2%)	3 (2%)
Marked	5	11 (6%)	11 (6%)

Percent in parentheses.

Interobserver differences in subjective scoring of PET scans by two independent readers blinded to angiographic and clinical data. Results are tabulated according to the maximum difference in scores assigned to each region by the two readers. Only one reading was available for two patients.

may be blunted by the partial volume effect which is a function of camera resolution.

PET defect severity correlated significantly with arteriographic stenosis severity ($r_s=0.77 \pm 0.06$). Linear regression yielded the equation:

$$\text{predicted SFR} = 4.14 - 0.70 (\text{PET defect rank})$$

with standard errors for the coefficients of 0.14 and 0.04, respectively. As above, this equation is provided for description rather than for calculations. As for Figure 3, top, mean values are used for clarity; regression was performed with the raw data. The problem of false-positive scans is described below.

Special Cases and Exceptions

One patient with a long intramyocardial portion or "muscle bridge" of the proximal left anterior descending artery had a moderate PET defect of the anterolateral wall. Two patients had defects of the resting PET scan which normalized with stress; one of these two patients had an arterioatrial fistula; the other had no evident coronary disease.

Results of nine patients deviated significantly from the pattern. Two patients with minimal stenosis severity ($\text{SFR} \geq 4$) had PET defects with scores more than 2. One with a stress PET defect score of 4.5 reported smoking five cigarettes immediately before the imaging. A repeat scan performed after the patient quit smoking was normal. The other patient with a PET defect score of 3 had undergone recent transluminal coronary angioplasty with subsequent angiographic dissection of the artery supplying the region of the PET defect, suggesting early restenosis or closure.

Seven patients with significant CAD ($\text{SFR} < 3$) had PET scores less than 2 or no defect. None of these seven cases involved proximal disease; in five, SFR was greater than 2.5. Mild LAD and diagonal lesions were more often missed than mild disease of other arteries, possibly due to diffi-

culty distinguishing normal apical thinning from mild perfusion defects.

PET Defect Location Compared With Site of Coronary Disease

PET defect location was compared to arteriographic localization for each patient. Results for patients with one-vessel disease are shown in Table 1. For patients with multivessel disease, 55 of 77 had multiple PET defects. In patients with mild or significant right and left circumflex coronary stenoses, five of 11 inferoposterior defects had associated lateral defects. In combined LAD-RCA disease, 11 of 13 patients had both anterior and posterolateral defects. Overall, anterior PET defects were associated with LAD or diagonal disease and posterior defects were associated with either left circumflex or right coronary disease.

Rest PET Defects Compared With Myocardial Infarction

Sixty-six patients had a clinical diagnosis of previous myocardial infarction. Fifty-one (77%) of these had resting PET defects and 18 of these had additional or more severe defects with stress. Fifteen patients with previous infarction had normal rest scans. Of these 15 exceptions, eight had undergone acute intervention with intravenous or intracoronary thrombolytic agents and/or transluminal balloon coronary angioplasty. Another five of the exceptions had non-Q wave infarctions only. The remaining two had well-developed collaterals.

Rest PET defect severity was less than two in 100 of 127 patients (79%) with no clinical diagnosis of myocardial infarction. Eight of the 27 exceptions had complete occlusions of at least one epicardial coronary artery. Three had regional wall motion abnormalities documented by gated nuclear or contrast ventriculography. Another eight had severe coronary stenoses, with SFR values less than two. There was no evidence of previous infarct in the remaining eight patients with abnormal rest scans; in two of these eight patients, scans normalized with stress, and the remaining six had abnormal stress scans as well.

Interobserver Differences in PET Scan Interpretation

In 82% of rest scans and 83% of stress scans, the two numeric scores were in agreement (Table 2). For 89% of patients, readers agreed on the overall interpretation of the presence (PET score ≥ 2) or absence of defects (PET score < 2) in the rest/stress scans. Disagreement most often involved the apex and inferoposterior wall. Forty-eight of 75 rest scans with identical readings were normal, and 40 of 59 stress scans with identical readings were normal.

Comparison With Thallium Scintigraphy

This study did not specifically compare PET imaging to other, more widely available, methods such as

²⁰¹Tl scintigraphy. Available data are not directly comparable because of the limitations of sensitivity/specificity analysis described in the introduction.

One recent study, by Zijlstra and colleagues,³⁰ reported the sensitivity and specificity of exercise thallium compared with radiographic coronary flow reserve in 38 patients with one-vessel disease. It is not directly comparable because of major differences in methods, including binary classification, number and selection of patients, coronary flow reserve compared with stenosis flow reserve, and exercise compared with dipyridamole stress. However, this is the only previous study, to our knowledge, in which imaging data are compared with a continuous scale of flow reserve (FR), permitting indirect comparison to the present results. 1) For moderate to severe stenoses (FR < 3), 72% (18 of 25) of thallium scans compared with 94% (108 of 115) of PET scans were negative. 2) For intermediate stenoses (FR = 3–4), 0% (0 of 9) of thallium scans compared with 49% (18 of 37) of PET scans were positive. 3) For minimal stenoses (FR ≥ 4), 100% (4 of 4) of thallium scans compared with 95% (39 of 41) of PET scans were negative. Three categories were compared because the small number of patients in the thallium study did not permit finer divisions, and correlation coefficients were not available for the thallium data. The intermediate range of 3–4 is used for simplicity, but it closely approximates the 95% confidence interval of stenosis flow reserve at the cut-off value of 3.4–3.5 established by other investigators.^{30,31} This comparison is limited because of the small number of thallium patients, especially in the range of normal and less severe disease; the specificity of thallium may be overestimated because of the small proportion of women, reducing the effect of attenuation artifacts.

Comparison of ⁸²Rb with ¹³N Ammonia

Images obtained with ⁸²Rb and ¹³N ammonia tracers were qualitatively similar. The two false positive cases included one ¹³N ammonia and one ⁸²Rb image. Of the seven false negative scans, five were ammonia scans and two rubidium. Thus, 79 of 82 rubidium images and 105 of 111 ammonia images were consistent with the arteriographic results. These ratios were not significantly different ($p = 0.73$).

Discussion

The accuracy of positron perfusion imaging of the heart has been reported in previous studies of the feasibility of clinical dipyridamole-PET imaging. Schelbert and colleagues¹⁶ compared PET scan results to percent diameter narrowing and found sensitivity and specificity values of 97% and 100%. According to standard statistical tables,³² the lower limits of the 95% confidence intervals for these values are 84% and 75%, respectively. In a study of 50 patients by Gould et al,¹⁷ PET scan results were compared with quantitative arteriographic stenosis flow reserve, and sensitivity and specificity were found to be 95% and 100%. The corresponding

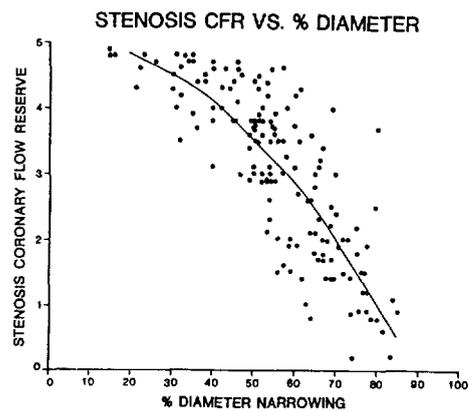


FIGURE 4. Plot of the relation between stenosis flow reserve and percent diameter narrowing, both calculated from quantitative arteriographic measurements, in the first 100 patients. Because percent diameter narrowing is only one of several factors used to calculate stenosis flow reserve, the scatter in this relation indicates the importance of those factors other than relative diameter that influence flow impedance of a stenosis.

lower limits of the 95% confidence intervals are 77% and 66%. The lower limits of the 99% confidence intervals are 71% and 56%. The overlap of these wide confidence intervals with the sensitivity and specificity values reported for planar thallium imaging, and even electrocardiographic exercise testing, indicate the need for larger numbers of patients for statistical accuracy.

The present study differs from earlier reports of perfusion imaging accuracy in the combined use of quantitative arteriographic stenosis flow reserve rather than percent diameter narrowing as the gold standard, the large number of patients, and the use of correlation rather than binary sensitivity-specificity analysis.

Stenosis Flow Reserve Compared With Coronary Flow Reserve

It is important to distinguish stenosis flow reserve,³³ which is calculated from static quantitative arteriographic dimensions, compared with coronary flow reserve, which is derived from direct measurement of the instantaneous ratio of hyperemic to rest flow. Coronary flow reserve depends on perfusion pressure, coronary venous pressure and/or arteriolar tone, and strength of the hyperemic stimulus; two stenoses of exactly the same geometry may have entirely different values of coronary flow reserve in different patients, or even in the same patient under different hemodynamic conditions. SFR, in contrast, is independent of hemodynamic conditions. It describes the conductance of the stenosis itself as if the arterial segment were excised and studied *in vitro* under controlled conditions. In the present application, this feature is advantageous because it allows comparison between patients. Neither measurement is superior; each

measures a different aspect of the stenosis, and each is applicable to a different clinical question.

Stenosis Flow Reserve Compared With Diameter Narrowing

The advantages of SFR over percent diameter narrowing, including the use of all relevant dimensions and absolute dimensions to allow for diffuse disease, have been described previously.²¹ To assess the importance of dimensions other than percent diameter narrowing that enter into the equation for stenosis flow reserve, calculated SFR was plotted as a function of percent diameter narrowing for the first 100 patients (Figure 4). Further patients were not included because of overlap of data points. The scatter in this relation represents the effect of factors other than relative diameter, such as length, absolute cross-sectional area, and expansion angle, that determine stenosis flow reserve.

These data reveal important limitations of the use of percent diameter narrowing as the sole indicator of stenosis severity, even when it is measured accurately. For arteries with 50% diameter narrowing, stenosis flow reserve ranges from 2.8 to 4.5. The spread is even wider for 60% narrowing. Many stenoses with more than 50% diameter narrowing have only mild or minimal reduction in SFR. Of 107 stenoses with more than 50% diameter narrowing, 30% had only mild SFR reduction ($SFR \geq 3$), and 8% had nearly normal coronaries ($SFR \geq 4$). Thus, true-negative perfusion scans associated with such lesions would be labeled as false-negative, if 50% diameter reduction alone were used to define significant coronary disease. In some studies, the criterion for significant coronary stenoses is 75% diameter narrowing. This cut-off point, or even 70% diameter narrowing, classifies a large number of stenoses with a significantly reduced SFR as negative. One third of stenoses with less than 75% diameter narrowing had significantly reduced stenosis flow reserve ($SFR < 3$), and 16% of these were severely narrowed ($SFR < 2$). As a result, true-positive scans associated with such lesions would be labeled as false-positive, were 75% diameter narrowing alone used to define significant coronary disease.

PET Defect Severity Compared With Stenosis Severity

PET defect severity correlated significantly with arteriographic stenosis severity in both the regional and patient-by-patient analysis. However, there was considerable scatter in these relations which may be attributable to the subjective scoring of PET defects or other limitations described below.

Rest PET Compared With Myocardial Infarction

The relation between PET defects and myocardial infarction has been previously described in a smaller group of patients.³⁴ The present results confirm that resting perfusion defects seen by PET correspond to clinical myocardial infarction.

Interobserver Agreement

Interobserver disagreement occurred primarily in scans of patients with mild coronary disease and those with small defects. The finding of 75% and 76% identical or essential agreement for rest and stress scans, respectively, is comparable with the 79% exact or essential interobserver agreement reported for ²⁰¹Tl images with a slightly different analytic method.²⁷

Potential Limitations

The use of a subjective scoring method for PET defect severity most likely accounts for much of the scatter in the relations in Figure 3. Quantitative methods for describing PET defect severity have been described, such as measurement of relative myocardial perfusion reserve.³⁵ However, this technique was not practical for the large number of patients in the present study because it requires subjective border delineation for regional analysis and assumes the presence of a normal region of myocardium in each patient. Technical limitations of quantitative PET imaging include cardiac motion, patient motion, partial volume errors, and decreased extraction of perfusion tracers at high flows.^{36,37} Subendocardial infarction may add to apparent error by introducing a partial-thickness perfusion defect without a correspondingly severe stenosis in the supply artery.

Stenoses in series may not have been accurately assessed. Only the single most severe stenosis was used to represent each artery because stenoses in series do not necessarily behave as additive resistances, due to intervening branches, and criteria for quantitative analysis of such lesions have not been established.

Anatomic variations in the coronary tree and overlap of perfusion beds limited the accuracy of matching each stenosis to a corresponding defect. For this reason, an additional analysis was performed to compare results for individual patients irrespective of defect location. This effect would tend toward underestimation of the relation between PET defect and stenosis severity by contributing to scatter. In addition, variation in perfusion bed size may cause arteries with equally severe stenoses to have variable sizes of PET defect.

Stenosis flow reserve may not correspond to PET perfusion reserve in the presence of altered physiologic conditions such as very high or low perfusion pressure and heart rate, collateral flow, increased resting flow, ventricular hypertrophy, abnormal venous pressure, or inadequate vasodilatory stimulus.³⁸ Although direct measurement of coronary flow reserve reflects these conditions, except for collateral flow, it may not be advantageous because hemodynamic conditions are likely to change between the times of catheterization and PET imaging.

Summary

Traditionally, noninvasive tests for the detection of coronary artery disease have been compared with percent diameter stenosis using binary classification and sensitivity-specificity analysis.^{1-4,39} Recent analyses^{5,6,8,11,40} have indicated the need for comparison to a more accurate gold standard and the use of continuous rather than binary outcome variables. In the present study, subjective PET defect severity and quantitative arteriographic stenosis flow reserve, a more physiologic gold standard, were compared over the full spectrum of coronary disease severity. Results indicate that subjective severity of regional PET perfusion defects correlates significantly with the calculated stenosis flow reserve of the corresponding coronary arteries.

Acknowledgments

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