

# PUBLIC SUBMISSION

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**Docket:** NRC-2020-0141

Reporting Nuclear Medicine Injection Extravasations as Medical Events

**Comment On:** NRC-2020-0141-0004

Reporting Nuclear Medicine Injection Extravasations as Medical Events; Notification of Docketing and Request for Comment

**Document:** NRC-2020-0141-DRAFT-0335

Comment on FR Doc # 2020-19903

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## Submitter Information

**Name:** Robert Van Arnam

**Address:**

300 Fayetteville Street  
Raleigh, NC, 27607

**Email:** rvanarnam@williamsmullen.com

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## General Comment

Commissioners - Please see the attached letter and exhibits

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## Attachments

November 12 2020 Letter to NRC-ID NRC-2020-0141

ACMUI 2008-12-18 Transcript\_extravasations discussion only

ACMUI 2009-05-08 Transcript\_extravasations discussion only

Robert C. Van Arnam  
Direct Dial: 919.981.4055  
rvanarnam@williamsmullen.com

November 12, 2020

U.S. Nuclear Regulatory Commission  
Washington, DC 20555-0001

**Re: Reporting Nuclear Medicine Injection Extravasations as Medical Events: Public Comment Regarding Docket ID NRC-2020-0141**

Dear Commissioners:

I write to you and particularly to your general counsel on behalf of the Petition (Docket ID NRC-2020-0141) and ask that the outdated reporting exemption be lifted. In many ways this letter could be a closing argument to a jury considering liability for the failure to meet the standard of care.

I am not a disinterested advocate; I represent the Petitioner Lucerno Dynamics in other matters. But I am also a lawyer whose grandparents, wife, niece and college friends have died from, or been affected by cancer. But today I speak not just for them but for all patients and their loved ones, to ensure that treatment with radiopharmaceuticals is safe and properly disclosed. As a threshold matter, any misapplication of toxic materials even at lower levels is something the treating physician *and* patient should know. When considering this matter, please ask yourself, if the affected patient was you, your spouse or child, wouldn't you want to know? Wouldn't you demand to know? And what would you do later if you discovered the facts surrounding this event had been withheld? These are simple questions with only one answer.

Having proven that extravasations are no longer unavoidable or undetectable [1], these incidents are indistinguishable from other cases of inadvertent exposure to radiopharmaceuticals that are currently required to be reported. The NRC and medical communities are on notice of the adverse effects from extravasations and, as such, cannot in good faith maintain a 40-year-old policy and intentionally withhold that knowledge from patients. That is not the standard of care. I ask that when considering the Petition and exemption, you follow the science but also think of the people affected. This is not and should not be considered an academic exercise.

The NRC defines nuclear safety culture as a "commitment by leaders and individuals to emphasize safety over competing goals to ensure protection of people and the environment." In other words, safety comes first and overcomes any minor burdens associated with detection and reporting. The NRC affirmed its mission by stating in the August 3, 2000 Federal Register (65 FR 47654) that the NRC has an important role "assuring accurate delivery of radiation doses and dosages to patients", rejecting the notion that the NRC should not regulate patient radiation safety. In considering the Petition, the NRC therefore cannot ignore its own mission statement but must be driven by it.

The Petition opponents (medical communities, SNMMI, Health Physics Society) ask the NRC for permission to self-regulate, and then unsurprisingly claim that since nothing has changed

in 40 years, the historical exemption should be maintained. Based on this outdated analysis, the opponents claim extravasations are unavoidable, unpredictable and cause no harm. These arguments appear from the evidence presented to be simply erroneous. First, SNMMI cannot claim extravasations are an unavoidable problem at the same time it forms an initiative to address them. The latter action belies the former position. As a lay person, that position sounds to me like the medical community is saying: (1) as a party with a conflict of interest we will form a committee to answer a question for which we already have an answer because we don't want to know the extent of this issue; and (2) additional reporting means a little more work, and thus we should be excused from additional reporting even if extravasations occur frequently and are known to be caused by numerous factors external from the patient and within our control (i.e. technique, technologists and tools). [1] The unassailable evidence in empirical, peer-reviewed studies from US and Australian centers shows that radiopharmaceutical extravasations are indeed avoidable. [1-4] Second, with new technology now available, detection is possible and without undue burden and cost. The result is that extravasations are predictable and with appropriate actions can be reduced to a very low level.

Third, and most significantly, extravasations are not benign. The opponents, including the HPS, state in opposition that: "there is no evidence that infiltration of radiopharmaceuticals carries **any** health consequences for the patient or the general public" (emphasis added). That statement is verifiably and even arrogantly false. While there is no evidence extravasations benefit patients in any respect, the NRC has been provided over 50 peer-reviewed references demonstrating how a diagnostic radiopharmaceutical extravasation has or could affect images and patient care. These include misdiagnoses, incorrect assessments, unnecessary interventional procedures, and additional repeat imaging of extravasated patients, all of which could have been avoided had the patient not been extravasated. Indeed, the public statement by SNMMI/SNMMI-TS/ASNC/ACNM confirms as much as they affirm that extravasations frequently occur and that "the Society recognizes the effect that extravasation of diagnostic radiopharmaceuticals may have on the quality of diagnostic images, particularly on quantitative studies."

In addition to the known effects to diagnostic imaging and patient care, the NRC and medical communities also know that therapeutic extravasations and many diagnostic extravasations can result in high doses to tissue and that the effects of such events may not be known for long periods of time. The medical community knows the risk-informed regulatory reporting limit of 0.5 Sv. Furthermore, the SNMMI's own publication on the NRC website (dated 2001) states that "Deterministic effects include reddening of the skin, sterility, cataracts, radiation sickness, and even death if the dose is high enough. Deterministic effects occur only after relatively high dose levels that exceed the threshold for those effects, usually a dose on the order of 100 rem (1Sv)." The SNMMI and NRC are aware that diagnostic and therapeutic extravasations can exceed this threshold and as a result, patients are vulnerable to adverse tissue effects. Yet with all of this knowledge, the community is not performing dosimetry to assess these extravasated doses. They are not following these patients for an appropriate period of time. They are not sharing this information with their patients. Reporting of these significant extravasations should be the standard.

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Finally, the NRC has been aware of this issue for years. Not only was the SNMMI 2001 Publication on the NRC website, but in 2008 and 2009, the NRC met with ACMUI to consider if the 1980 policy should be eliminated. At that time, NRC heard testimony where ACMUI members admitted that: these events happen frequently; if they took more care they could be prevented; and that some of the doses are well beyond 1.0 Sv. But in response, the NRC did nothing, agreeing with the ACMUI's illogical, but convenient, recommendation to retain the reporting exemption (transcripts from these meetings attached). Presented with this issue yet again, the NRC must act.

With current and comprehensive information on extravasations, the NRC and doctors are on notice that extravasations are common, detectable and harmful to patients. Willful blindness is no longer an option, and neither NRC nor doctors can credibly rely on self-interested and outdated information to preserve the exemption. Denying the Petition presents undeniable risks to patients who will discover that the potential harm from extravasations were known and withheld. I appreciate the opportunity to add to the public comment.

Very truly yours,

  
Robert C. Van Arnam

## References

1. Wong, T.Z., et al., Quality Improvement Initiatives to Assess and Improve PET/CT Injection Infiltration Rates in Multiple Centers. *J Nucl Med Technol*, 2019. **47**: p. 326-331.
2. Kiser, J.W., et al., Assessing and Reducing Positron Emission Tomography/Computed Tomography Radiotracer Infiltrations: Lessons in Quality Improvement and Sustainability. *JCO Oncology Practice*, 2020. **16**(7): p. e636-e640.
3. Currie, G.M. and S. Sanchez, Topical Sensor for the Assessment of Injection Quality for 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE Positron Emission Tomography. *J of Medical Imaging and Radiation Sciences*, 2020. **51**: p. 247-255.
4. Osborne, D.R., et al., Assessing and reducing PET radiotracer infiltration rates: a single center experience in injection quality monitoring methods and quality improvement. *BMC Med Imaging*, 2020. **20**(1): p. 3.

**Official Transcript of Proceedings**  
**NUCLEAR REGULATORY COMMISSION**

Title:           Advisory Committee on the Medical Uses of Isotopes

Docket Number:   (n/a)

Location:                 (telephone conference)

Date:                    Thursday, December 18, 2008

Work Order No.:    NRC-2577

Pages 1-101

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1 I realize that you have to take time out of your busy  
2 schedules to do those. But the management of NRC is  
3 held very accountable to making sure everyone has  
4 jumped through all the hoops on all of those periodic  
5 training requirements.

6 At this point, if Dr. Malmud will indulge  
7 me, I would be willing to take any questions from the  
8 committee members before we get started on general  
9 topics.

10 CHAIRMAN MALMUD: Are there any questions?

11 This is Malmud. Are there any questions?

12 (No response.)

13 MR. LEWIS: Thank you, Dr. Malmud. I will  
14 turn the meeting over to you.

15 CHAIRMAN MALMUD: Thank you. We have the  
16 next item on the agenda, which will be Cindy Flannery.

17 Am I correct, Cindy?

18 MS. FLANNERY: Yes. Cindy Flannery. The  
19 topic of this first discussion is NRC's position on  
20 the applicability of the medical event reporting  
21 criteria for an event that was reported to the NRC  
22 involving an infiltration of F-18 of FDG.

23 NRC staff's objective here today is to get  
24 ACMUI's input on whether NRC staff should pursue a  
25 change to our current position on the lack of

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1 reportability of infiltrations of dosages that may  
2 result in doses that exceed the dose threshold in the  
3 medical event reporting criteria -- that is, 50 rem to  
4 an organ or tissue.

5 An event was reported earlier this year as  
6 possible medical event. 3.6 millicuries of F-18 FDG  
7 was infiltrated into the anacubital dermis adjacent to  
8 the left elbow. The dose of the tissue was estimated  
9 to range somewhere between 200 millirem and 96 rem,  
10 and it was based on assumptions such as the entire  
11 dose was infiltrated into a tissue of 60 cubic  
12 centimeter volume sphere using a soft tissue density  
13 of 1.06 gram per cubic centimeter with a range of mean  
14 resonance time of .006 to 2.6 hours.

15 So just a little bit more background on  
16 this, the needle was carefully checked for  
17 infiltration using a 10 milliliter flush and a 100  
18 milliliter infusion prior to injection of the F-18  
19 FDG. The infiltration was discovered upon image  
20 acquisition one hour after the administration, and,  
21 unfortunately, the biological parameters were not  
22 measured, so it lead to a very large and varied  
23 absorbed dose estimates, as listed in slide 3.

24 But there were no identified adverse  
25 effects. There was nothing to suggest any kind of a

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1 radiation injury.

2 The licensee did file a report 30 days  
3 after the event, and they stated that, "Because the  
4 technologist noted the diffuse localization of the F-  
5 18 FDG, it seems likely that much of the administered  
6 dose did not -- or, I'm sorry -- did get into the  
7 vein, leaving less than 3.6 millicuries to irradiate  
8 the local area."

9 NRC's internal dose assessor did review  
10 the licensee's dose estimates, as provided on slide 3,  
11 and found this to be reasonable. Using a different  
12 method, NRC's calculations were slightly lower, but,  
13 as I said, they were certainly reasonable.

14 Now, as far as the outcome, the event was  
15 later retracted because NRC staff determined that an  
16 infiltration does not require reporting as a medical  
17 event. Based on some supplementary information that  
18 supported the previous equivalent regulation -- 35.33  
19 -- which states -- and it's in 45 Federal Register  
20 31703, May 14, 1980, "Extravasation is the  
21 infiltration of injected fluid into the tissue  
22 surrounding a vein or an artery. Extravasation  
23 frequently occurs in otherwise normal IV or intra-  
24 arterial injections. It is virtually impossible to  
25 avoid. Therefore, the Commission does not consider

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1 extravasation to be a misadministration."

2           So based on these excerpts from the  
3 statement of consideration that I just quoted, it was  
4 staff's determination at that time that this case did  
5 not qualify as a medical event. It has always been  
6 NRC's position that infiltrations do not constitute a  
7 medical event.

8           But that position has been based on the  
9 fact that diagnostic dosages, like technetium-99m,  
10 that were typically used in nuclear medicine at the  
11 time are gamma emitters of relatively low energy and  
12 low risk and wouldn't exceed the dose thresholds that  
13 are in the medical event criteria.

14           The language in the FRN is not really  
15 based on a distinction between diagnostic and  
16 therapeutic administrations, but, rather, on the fact  
17 that some of that, such as infiltrations, are an  
18 integral part of the procedure, and so their  
19 occurrence must be viewed as expected.

20           At the time that this FRN was published,  
21 higher energy radiopharmaceuticals, like PET  
22 radiopharmaceuticals, were just not being used. This  
23 is from 1980, as I mentioned before.

24           F-18 is a diagnostic administration, but  
25 because of the higher energies that can now result in

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1 a dose to the surrounding tissue exceeding 50 rem,  
2 when doses are infiltrated, NRC is trying to determine  
3 whether there is any justification based on safety  
4 significance to change NRC's policy for these new NARM  
5 materials, which are now under our regulatory  
6 authority, and also the applicability of the medical  
7 event criteria for infiltrated dosages.

8 And just to take it one step further,  
9 should there be a requirement for reporting an  
10 infiltration of a therapeutic administration, that is  
11 something that also has not been considered before.

12 So that concludes my opening of the  
13 discussion.

14 CHAIRMAN MALMUD: Thank you, Cindy.

15 Any comments or discussion regarding the  
16 issue of infiltration of F-18 FDG? I heard someone  
17 click on or click off.

18 MEMBER THOMADSEN: That is Bruce joining  
19 you. Sorry I am late. I had a patient who was  
20 considerably late today.

21 CHAIRMAN MALMUD: Thank you for joining  
22 us. Cindy just presented the material regarding the  
23 infiltration of F-18 FDG and therapeutic  
24 radiopharmaceuticals. I was asking the group if there  
25 are any comments regarding her presentation.

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1 VICE CHAIRMAN VETTER: Dr. Malmud, this is  
2 Dick Vetter.

3 CHAIRMAN MALMUD: Dr. Vetter?

4 VICE CHAIRMAN VETTER: I just wanted to  
5 point out that there is -- it's a bit old, but there  
6 is a publication that looked at infiltrations of  
7 radiopharmaceuticals back in 1994, Castronovo, et al.,  
8 and the -- they looked at infiltration of various  
9 volumes, various volumes of tissue, etcetera.

10 And just as an example, maximum specific  
11 activity for a thallium -- let's see, infiltrations of  
12 thallium at the maximum specific activity available in  
13 two gram volume of tissue, worst case possible, would  
14 produce skin radiation burden of 417 to 463 rads. If  
15 you look at the table in that particular publication,  
16 which I can share with the staff if they don't have  
17 it, the doses range from about 40 rads to over 500,  
18 almost 600.

19 So the doses from infiltration are  
20 potentially significant. In fact, they are quite a  
21 bit higher than that particular PET issue that she  
22 outlined.

23 CHAIRMAN MALMUD: Thank you.

24 MEMBER NAG: Hello. Sorry to be late on  
25 the phone. This is Dr. Nag calling in.

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1 CHAIRMAN MALMUD: Thank you, Dr. Nag. We  
2 just discussed the infiltration of F-18 FDG  
3 therapeutic radiopharmaceuticals. And Dr. Vetter  
4 responded that this already had been discussed about  
5 10 years ago or so in a publication by Dr. Castronovo,  
6 where the infiltrations resulted in, if I am quoting  
7 correctly, an even greater radiation burden than these  
8 mentioned. Am I correct, Dr. Vetter?

9 VICE CHAIRMAN VETTER: Yes, that is  
10 correct. Yes, that's correct.

11 CHAIRMAN MALMUD: And, therefore -- this  
12 is Malmud again. And, therefore, the issue really was  
13 presented, dealt with, and probably need not be dealt  
14 with again. Is that your feeling, Dr. Vetter?

15 VICE CHAIRMAN VETTER: Well, I wouldn't  
16 necessarily say it doesn't need to be dealt with, but  
17 it has been dealt with in the literature in the past.  
18 I don't know if the NRC has ever looked at that  
19 literature, but it has been dealt with in the past in  
20 the literature, and the doses reported are  
21 considerably higher than that particular case that was  
22 outlined.

23 So I wouldn't view that particular case as  
24 being particularly egregious when compared to what  
25 apparently happens routinely in the injection of

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1 radiopharmaceuticals.

2 CHAIRMAN MALMUD: This is Malmud again.  
3 Therefore, Dr. Vetter, what would your response be to  
4 the question raised by Cindy Flannery? And the  
5 question in the last slide is: considering the higher  
6 doses from the use of NARM, should NRC change its  
7 position to now regard infiltrations as MEs if the  
8 resulting dose exceeds the dose limits of 10 CFR  
9 35.3045.

10 VICE CHAIRMAN VETTER: My opinion is that  
11 the -- that the practice should not be changed at this  
12 point in time. However, with the increased use of  
13 therapeutic radiopharmaceuticals, I think it is a  
14 subject that should be investigated, but nothing  
15 changed at this point in time.

16 MEMBER NAG: This is Dr. Nag. My  
17 viewpoint would be that this is somewhat akin to the  
18 seed migration issue for permanent implant. And that  
19 if in the -- if the injection of radioactive material,  
20 whether it's 125 ccs or, you know, NARM, if it is  
21 routine that some of it infiltrates out, and that this  
22 is something that happens in the normal course of a  
23 medical event, it should not -- I mean, the normal  
24 course of a medical administration, this should not be  
25 viewed as a medical event.

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1 CHAIRMAN MALMUD: Thank you, Dr. Nag.

2 Dr. Vetter, do you wish to make your  
3 recommendation into a motion?

4 VICE CHAIRMAN VETTER: I would be happy to  
5 do that. I move that the ACMUI recommend that the NRC  
6 not change its practice regarding the definition of  
7 infiltrations as medical events at this time.

8 CHAIRMAN MALMUD: Thank you.

9 Dr. Nag, are you seconding that motion?

10 MEMBER NAG: I will be seconding that  
11 motion, but I want to make sure that the following  
12 definition says that infiltrations are not medical  
13 events. I want to confirm that, please. Can someone  
14 confirm that?

15 CHAIRMAN MALMUD: I'll ask -- this is  
16 Malmud. I'll ask Dr. Vetter to confirm that in his  
17 motion.

18 VICE CHAIRMAN VETTER: Yes, I would accept  
19 that as a friendly amendment to the motion. But I  
20 think Cindy Flannery can confirm that that is the  
21 practice now.

22 CHAIRMAN MALMUD: And I'll ask Cindy, is  
23 that the practice now from your view?

24 MS. FLANNERY: Yes. This is Cindy  
25 Flannery. Yes, that is NRC's position based on that

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1 supplementary information.

2 CHAIRMAN MALMUD: Thank you, Cindy.  
3 Therefore, Dr. Vetter's motion stands, with Dr. Nag's  
4 seconding. Is there any discussion of the motion?

5 MEMBER EGGLI: This is Doug Eggli. I'd  
6 like to speak to the motion.

7 CHAIRMAN MALMUD: Thank you. Dr. Eggli?

8 MEMBER EGGLI: There are -- infiltrations  
9 just always occur. If they were to become medical  
10 events, the NRC would be flooded with more medical  
11 events than it could manage. But, in addition, the  
12 radiation is a function of the volume of distribution.

13 Obviously, the smaller the volume of the infiltration  
14 the higher the local radiation dose. In 30 years of  
15 clinical practice, I have seen lots and lots and lots  
16 of infiltrations. I have never seen an adverse  
17 clinical outcome.

18 Unlike non-radioactive iodinated  
19 radiographic contrast, which often has significant  
20 local complications when infiltrated, I have never  
21 seen an adverse outcome from a radiopharmaceutical  
22 infiltration in my clinical practice. And I strongly  
23 support the motion that they should be left in their  
24 current status as not medical events.

25 CHAIRMAN MALMUD: Thank you, Dr. Eggli. I

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1 would second your observation, in that 37 years of  
2 nuclear medicine practice I have not seen a negative  
3 outcome as a result of an accidental infiltration of a  
4 diagnostic radiopharmaceutical.

5 Are there other comments or discussions  
6 regarding the motion?

7 MEMBER LIETO: This is Ralph Lieto.

8 CHAIRMAN MALMUD: Yes, Mr. Lieto.

9 MEMBER LIETO: I would also support that  
10 the current policy statement of the NRC be maintained.  
11 And maybe what we ought to do is just say that we  
12 reaffirm it with the, you know, current terminology of  
13 replacing misadministration with medical event.

14 The only thing I would maybe suggest in  
15 terms of change is that I don't think extravasation is  
16 a frequent occurrence in nuclear medicine. Otherwise,  
17 you'd have patients being repeated beaucoup times, and  
18 it is a very uncommon occurrence. So I would say that  
19 we just reaffirm the current statement as it -- that  
20 was postulated back in 1980.

21 CHAIRMAN MALMUD: This is Malmud. Mr.  
22 Lieto, are you willing to accept and support Dr.  
23 Vetter's motion?

24 MEMBER LIETO: Yes, because it basically  
25 reaffirms that.

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1 CHAIRMAN MALMUD: Thank you.

2 MEMBER EGGLI: This is Doug Eggli. I'd  
3 like to comment again in response to Ralph's last  
4 statement.

5 CHAIRMAN MALMUD: Please do.

6 MEMBER EGGLI: I think that complete  
7 infiltrations are not as common, although I see them  
8 with some regularity, particularly if you have a very  
9 young technologist staff. However, partial  
10 infiltrations, as a needle flips in and out of a vein,  
11 are really quite common and have neither impact on the  
12 diagnostic quality of the study, nor long-term adverse  
13 impact on the patient.

14 MEMBER LIETO: I accept that  
15 clarification.

16 CHAIRMAN MALMUD: Thank you, Mr. Lieto.

17 Any other discussion of the motion on the  
18 floor?

19 MR. STABIN: Yes, this is Mike Stabin. I  
20 would note that even though this has been treated once  
21 or twice in the literature, it is very difficult in  
22 these situations to establish what you mean by "the  
23 dose." When you're talking about dose to a standard  
24 organ, it is pretty easy to define it.

25 But in these cases, as was mentioned by

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1 someone else, it depends on the volume that you  
2 assume, the distance from that volume where you assign  
3 dose, and so there is not really a good standardized  
4 model for people to assign a dose to report.

5 CHAIRMAN MALMUD: Thank you. Are you also  
6 supportive of the motion?

7 MR. STABIN: I don't have a position on  
8 the motion. I just wanted to contribute that comment,  
9 that this would be difficult at the moment I think for  
10 people.

11 CHAIRMAN MALMUD: Thank you. I think we  
12 all agree with your observation. Are there any other  
13 comments?

14 MEMBER FISHER: Dr. Malmud?

15 CHAIRMAN MALMUD: Yes. Who is speaking,  
16 please?

17 MEMBER FISHER: This is Darrell Fisher. I  
18 would like to follow up on a question raised by Cindy  
19 Flannery and ask for your experience and the  
20 experience of others, Dr. Eggli in particular. She  
21 asked about the case in which a therapeutic  
22 administration goes awry in the same way with a high-  
23 dose radionuclide such as Yttrium-90, Iodine-131, or  
24 even an alpha emitter, when those infusions become  
25 more common.

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1           And should the dose be very much greater  
2 as a result of an injection of this type? What would  
3 be your opinion?

4           CHAIRMAN MALMUD:     Are you asking me  
5 specifically?

6           MEMBER FISHER: Yes. And Dr. Eggli.

7           CHAIRMAN MALMUD: Thank you. I have not  
8 had experience with an infiltration of a therapeutic  
9 dose. I have been fortunate in my practice in that  
10 the therapeutic doses that we have used have been  
11 carefully administered by experienced personnel, and,  
12 therefore, the therapeutic doses have not infiltrated.

13           Having said that, I would also comment  
14 that Dr. Eggli's observation is a valid one with  
15 regard to diagnostic doses, and they not infrequently  
16 partially infiltrate.

17           Now, getting back to the question of the  
18 therapeutic, the therapeutic may in fact result in a  
19 radiation burden which will manifest itself with some  
20 visible abnormality. But I have not, fortunately,  
21 seen that in my years of practice. The doses we used  
22 to use were of pharmaceuticals such as P-32-containing  
23 pharmaceuticals.

24           More recently, of course, we are now into  
25 other forms of therapeutics, and there is a

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1 theoretical possibility that we will see some untoward  
2 effect from an infiltration of a therapeutic dose.  
3 However, I cannot personally speak to that experience.

4 Perhaps Dr. Eggli may.

5 MEMBER EGGLI: This is Doug Eggli. I  
6 share Leon's good fortune of never having had an  
7 intravenous therapy dose infiltrate. Just as a  
8 practice, I think our concern here is beta emitters  
9 being extravasated in the soft tissue as opposed to --  
10 or alpha emitters as opposed to gamma emitters. But  
11 we really take a whole different level of care in  
12 establishing our IV lines on therapeutic data emitters  
13 than you do typically on routine diagnostic studies.

14 And I would think that you will find that  
15 the incidence of infiltration of therapeutic beta  
16 emitters or other -- or alpha emitters, when they  
17 become used, is going to be -- that I think is going  
18 to be fairly uncommon because of the quality of the IV  
19 that we establish to do that.

20 When you inject a diagnostic  
21 radiopharmaceutical, they are often simply done with a  
22 straight stick of a needle. And you can perforate the  
23 far side of a vein or partially perforate the far side  
24 of the vein. If you get a good IV running and you run  
25 in 4- or 500 ccs of fluid prior to the administration

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1 of your therapeutic dose, I think the chances that you  
2 have a malfunctioning IV are likely to be detected  
3 before you administer a therapy dose.

4 And we typically put in a fairly large  
5 volume of non-radioactive fluid through an IV where we  
6 plan to give a therapy, just to make sure that it  
7 really is where we -- a good IV, and that we are not  
8 putting anything into the tissues.

9 You can put 10 or 20 ccs of fluid into the  
10 tissue and not notice it. It is much harder to put 4-  
11 or 500 ccs into the tissue and not notice it.

12 MEMBER NAG: This is Dr. Nag. I agree  
13 with you, Dr. Eggli. However, the question would be:  
14 if someone is not very conversant with the technique,  
15 and is going to be doing an infusion and puts in only  
16 20 or 30 ccs, and it is running well, and then start  
17 infusing a therapeutic dose, it is possible that it  
18 will not extravasate.

19 In that situation, what would the NRC do?  
20 I think that's the question that was being asked, or  
21 possibly that's a question that would be asked.

22 MEMBER EGGLI: This is Doug Eggli again.  
23 Again, I think the incidence of that would be  
24 uncommon. And, again, with the therapeutic data  
25 emitter, I think it might rise to the level of a

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1 medical event.

2 VICE CHAIRMAN VETTER: This is Dick  
3 Vetter. I just wanted to point out a subtle  
4 difference in the way diagnostic radiopharmaceuticals  
5 are administered versus therapeutic. In diagnostic,  
6 they are injected. In therapy, they are infused. And  
7 that's a huge difference.

8 As Dr. Eggli mentioned, during infusion it  
9 is very carefully -- the IVs are very carefully  
10 administered, and then a considerable amount of saline  
11 is used to make sure you have a patent IV. And some  
12 medical centers, even during the administration of the  
13 therapeutic radiopharmaceutical, will periodically  
14 interrupt the administration and administer some  
15 saline to make sure that the line continues to remain  
16 free.

17 So it is really two different -- totally  
18 different types of injection or administration.

19 MEMBER SULEIMAN: Yes. This is Orhan.  
20 Are we in fact discussing the therapeutic? I thought  
21 the question was really limited to the diagnostic. I  
22 have no trouble discussing the therapeutic, but does  
23 the NRC want it answered? And have we digressed?

24 CHAIRMAN MALMUD: Orhan, this is Malmud  
25 again. You are correct. The motion referred to the

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1 diagnostic. And if you wish to -- if there is an  
2 interest in discussing the therapeutic, I think that  
3 we can, but it might be best to first achieve closure  
4 on the diagnostic.

5 Are there any other comments regarding the  
6 diagnostic?

7 (No response.)

8 If not, may we move the motion forward?  
9 All in favor of the motion?

10 (Chorus of ayes.)

11 Are there any opposed to the motion?

12 (No response.)

13 Are there any abstentions?

14 (No response.)

15 Thank you. Therefore, the motion is  
16 approved unanimously regarding the infiltration of  
17 diagnostic radiopharmaceuticals.

18 We are getting static again. Could some  
19 -- those who are not talking -- thank you. Thank you.

20 The discussion regarding therapeutic  
21 radiopharmaceuticals I think was well summarized in  
22 the comments made by several of you. It is the  
23 practice in administering therapeutic  
24 radiopharmaceuticals to first establish an intravenous  
25 line, and to make certain of its patency.

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1           And that differs from the injection of a  
2 diagnostic radiopharmaceutical, which is, as correctly  
3 described, an intravenous injection without the prior  
4 establishment -- most often without the prior  
5 establishment of an intravenous line.

6           Now, therefore, a question arises, and  
7 that is this is a -- first, a statement. It is a  
8 common practice for us medically to establish an  
9 intravenous line or therapeutic doses that are given  
10 IV. Should this be a matter of written requirement  
11 that -- and, quite frankly, I am not certain if it  
12 already is or is not. Is anyone familiar with the  
13 regulations regarding the administration of  
14 therapeutic radiopharmaceuticals? Do we require an  
15 intravenous line?

16           MEMBER LIETO: The regulations do not.

17           CHAIRMAN MALMUD: Should they?

18           MEMBER LIETO: This is Ralph Lieto. I  
19 don't think we should enter into the practice, since  
20 things might change regarding that. I think the less  
21 we have in the regulations the better.

22           CHAIRMAN MALMUD: Thank you.

23           MEMBER SULEIMAN: This is Orhan. I would  
24 agree with Ralph. I mean, the route of administration  
25 may vary depending on the pathology, and so limiting

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1 it to one way of administering is going to cause  
2 problems.

3 CHAIRMAN MALMUD: Thank you. Are there  
4 any other opinions regarding that issue?

5 VICE CHAIRMAN VETTER: This is Dick  
6 Vetter. I agree with that as well. And, in fact, I  
7 am sure that the method of administration was worked  
8 out during development of the protocol. So it is  
9 probably already in the FDA literature on how the  
10 material should be administered.

11 CHAIRMAN MALMUD: Thank you. So with  
12 those opinions, we will lay the issue of the  
13 therapeutic radiopharmaceuticals to rest at the  
14 moment, and move on with the rest of our agenda, if  
15 that is agreeable with the participants in today's  
16 discussion.

17 MEMBER NAG: Yes, that is agreeable.

18 CHAIRMAN MALMUD: Thank you.

19 MS. FLANNERY: Dr. Malmud, this is Cindy  
20 Flannery.

21 CHAIRMAN MALMUD: Yes, Cindy.

22 MS. FLANNERY: I think we are also trying  
23 to get some input or feedback on how this applies to  
24 therapeutics. And I do want to just add one thing, a  
25 comment that Dr. Vetter made, that, you know, your

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1 therapeutic administrations are infused. And in this  
2 particular case, this F-18 was handled the same way.  
3 It was described at a 10 mL flush, and a 100 mL  
4 infusion was done prior to the injection.

5 So I understand that even when you have a  
6 line set up like that, to prevent it from happening,  
7 realize that it is incredibly rare, but as in this  
8 case there is that potential. So we would like to get  
9 some input on how this would apply to therapeutic  
10 administrations.

11 CHAIRMAN MALMUD: Thank you. May we have  
12 some opinions regarding how this should be ideally  
13 worded?

14 MEMBER EGGLI: This is Doug Eggli. Even  
15 though it was given through an IV line, and we give  
16 all of our PET doses through an IV line, there are IV  
17 lines and there are IV lines, and there are levels of  
18 care taken in establishment of the IV line that I,  
19 again, think are really quite different in therapeutic  
20 and diagnostic.

21 The quality of the needle catheter used, a  
22 butterfly versus an angiocath or some other form of  
23 internal catheter makes a great deal of difference in  
24 the quality of the line and the likelihood of an  
25 infiltration. So, again, I think that the likelihood

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1 in a therapeutic infusion is really very small.

2           However, we are infusing currently often  
3 beta emitters, and I am less concerned with gamma  
4 emitters than I am with the local radiation with beta  
5 emitters. And if we infuse and infiltrate a beta  
6 emitter in large quantities, it is conceivable we  
7 could see tissue damage.

8           I am not as -- I am not opposed to making  
9 a therapeutic infiltration of medical event, but I  
10 think it probably requires some more discussion about  
11 things I am probably not thinking about. But, again,  
12 I think it will be uncommon. And, again, let me say  
13 that not all IV lines are the same.

14           MEMBER NAG: This is Dr. Nag. The problem  
15 is that, how will you define -- for example, in other  
16 areas we say if it is more than 20 percent, you know,  
17 we have a number like 20 percent dose, how can you say  
18 that -- you know, how much infiltration? Like if one  
19 is infiltrated, obviously, that is not going to be a  
20 medical event. If the whole dose is infiltrated, I  
21 mean, that obviously would be a medical event. So how  
22 would you say how much of it infiltrated in terms of  
23 quantity? And that may be a difficult thing. It may  
24 need a separate discussion.

25           MEMBER EGGLI: This is Doug Eggli. I

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1 agree with you on that, Subir. But I think, again,  
2 the flag would probably be a function of local tissue  
3 exposure, and is there enough local radiation  
4 deposited that acute tissue injury is likely to occur.

5 MEMBER NAG: Again, that would be very  
6 hard to quantitate.

7 CHAIRMAN MALMUD: Gentlemen, may I ask if  
8 it would be an issue which we should bring to the  
9 ACMUI and discuss with regard to which type of  
10 material should be used for infusions of beta-emitting  
11 therapeutic pharmaceuticals, radiopharmaceuticals, so  
12 that we can discuss it at length.

13 I think the point that was made about a  
14 butterfly versus an intravascular catheter is  
15 relevant, because butterflies can infiltrate easily,  
16 particularly when there is arm movement by the  
17 patient. And whereas intra-caths, once established,  
18 of one type or another, generally are less likely to  
19 perforate the vessel.

20 So that this is an issue which may be  
21 worth discussing at the -- as an agenda item at the  
22 next ACMUI. Therefore, I am making a recommendation  
23 that it be discussed at the next ACMUI rather than  
24 attempting to resolve it on a conference call without  
25 having a chance to have thought it through with all of

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1 its ramifications. Is that acceptable to the  
2 committee?

3 MEMBER NAG: I would agree -- I would  
4 support that wholeheartedly.

5 MEMBER EGGLI: This is Doug Eggli. I  
6 agree.

7 CHAIRMAN MALMUD: Is there anyone that  
8 doesn't agree?

9 MEMBER SULEIMAN: This is Orhan. I would  
10 agree, but I think it's a much more complicated issue,  
11 and I am even hesitant to bring it up without more  
12 preparation, because somebody mentioned beta emitters  
13 versus gamma. I think you have to look and see that  
14 at some point you may see alpha emitters being  
15 approved in the U.S. And we are not talking about  
16 diagnostic here, we are talking about therapeutic and  
17 the optimum administration.

18 So it is very, very fuzzy to me, you know,  
19 where the -- where the practice of medicine and  
20 specific protocols come into play, and where the  
21 radiation dose excesses or events would come into  
22 play. So I think we should discuss it, but I am  
23 nervous about bringing it up without adequate  
24 preparation. Otherwise, the discussions could be in a  
25 very circuitous, neverending kind of mode.

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1 CHAIRMAN MALMUD: Orhan, I think you are  
2 right, but it points out once again the complexity of  
3 the issue, and, therefore, the fact that this  
4 important subject brought up by Cindy is better dealt  
5 with in a meeting of the ACMUI than on a conference  
6 call such as this.

7 MEMBER SULEIMAN: I agree.

8 CHAIRMAN MALMUD: Is there anyone who was  
9 opposed to delaying this to the next meeting of the  
10 ACMUI?

11 MEMBER GILLEY: This is Debbie. I am not  
12 opposed. I just wanted you to know I am on the call.

13 CHAIRMAN MALMUD: Thank you, Debbie. We  
14 are glad that you are on the call.

15 Therefore, recognizing that it is a  
16 potentially important issue, we will ask that it be  
17 included on the agenda for the next ACMUI. The result  
18 of the next ACMUI meeting may be that we will  
19 establish a subcommittee to look at it, because of its  
20 complexity. On the other hand, given the fact that it  
21 is brought to our attention today, it seems to me that  
22 we should bring it to the next ACMUI, so that we keep  
23 it on the agenda and deal with it as promptly as  
24 possible.

25 If that is acceptable with the committee,

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1 we will do that. If not, we will do whatever the  
2 committee recommends instead. Is it acceptable to the  
3 committee members?

4 (Several members respond in the affirmative.)

5 Thank you. Then, Debbie and Cindy, do we  
6 have any other items to discuss on today's agenda?

7 MS. FLANNERY: Yes, we have one more  
8 agenda item.

9 CHAIRMAN MALMUD: And Dr. Vetter? Dr.  
10 Vetter? Dick? Dr. Vetter? Is Dr. Vetter with us?

11 VICE CHAIRMAN VETTER: Am I with you now?  
12 I guess my mute was on.

13 CHAIRMAN MALMUD: Dick, I have to give a  
14 therapeutic dose right now. I am going to run out for  
15 five minutes and come back, so --

16 VICE CHAIRMAN VETTER: Okay.

17 CHAIRMAN MALMUD: -- could you take over  
18 for me?

19 VICE CHAIRMAN VETTER: As long as you make  
20 sure that that line is well administered, yes.

21 CHAIRMAN MALMUD: It's an oral dose,  
22 and --

23 VICE CHAIRMAN VETTER: Oh, it's an oral.  
24 Okay.

25 CHAIRMAN MALMUD: -- the practice of my

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1 the patient was scheduled for.

2 CHAIRMAN MALMUD: Thank you. May we move  
3 on?

4 Thank you very much, Mr. Lieto.

5 We will move on to the next item on the  
6 agenda. And Cindy Flannery is on for infiltration,  
7 infiltrations of therapeutic radiopharmaceuticals as  
8 medical events.

9 MS. FLANNERY: Well, this presentation is  
10 really just a continuation of a discussion we had at  
11 the December 18<sup>th</sup>, 2008 teleconference. And I will  
12 just briefly summarize that discussion and where we  
13 left off.

14 I have provided a description of an event  
15 involving infiltration of F-18 FDG, and it was  
16 reported to the NRC as a possible medical event  
17 because the dose to the tissue potentially exceeded  
18 the medical event criteria of 50 rem to the  
19 surrounding tissue.

20 I explain how the event was later  
21 retracted, because it is and has been NRC's position  
22 that infiltrations do not need to be reported to the  
23 NRC as medical events. And that is really based on  
24 supplementary information to a previous equivalent  
25 regulation which is 35.33. And that states, quote:

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1 Extravazation is the infiltration of injected fluid  
2 into tissues surrounding a vein or artery.  
3 Extravazation frequently occurs in otherwise normal  
4 intravenous or intra-arterial injections. It is  
5 virtually impossible to avoid. Therefore the  
6 commission does not consider extravazation to be a  
7 mis-administration, unquote.

8 So this supplementary information doesn't  
9 provide a distinction between diagnostic and  
10 therapeutic administrations. This language is also  
11 almost 30 years old. I think IV administrations of  
12 therapeutic radiopharmaceuticals are more common now  
13 than they were back then, and also now NRC has  
14 regulatory authority over NARM, which with its higher  
15 energies if infiltrated, it will result in a higher  
16 dose to the surrounding tissues than, say, something  
17 like technetium 99m.

18 So I think with all these things being  
19 taken into consideration, NRC staff felt that it was  
20 prudent to seek ACMUI input on whether we should  
21 reevaluate our current position on infiltrations.

22 CHAIRMAN MALMUD: Thank you for bringing  
23 that before us. Does anyone have any comments on the  
24 issue of therapeutic infiltrations? Dr. Eggli?

25 DR. EGGLI: As a person that does some of

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1 these things, I have mixed feelings about how it ought  
2 to be handled. We certainly - the vascular access we  
3 obtain for a therapeutic administration gets a whole  
4 different level of scrutiny than the vascular access  
5 we obtain for a diagnostic administration.

6 I will not push a radioactive treatment  
7 dose forward if I cannot draw blood back from the  
8 line. Now, that doesn't give you 100 percent  
9 assurance depending on how you catheterize the vein.  
10 A stainless steel needle can give you a blood return,  
11 but you have to tip the needle out. But however we  
12 almost never used butterflies anymore for treatment,  
13 and we use plastic catheters which are far less likely  
14 to produce a blood return with a partial  
15 extravazation.

16 So our efforts at making sure we really  
17 have a good line before we push a therapeutic agent  
18 into a vein is a whole different level of assurance  
19 when we administer a diagnostic pharmaceutical for the  
20 very reason that you mention here, that the potential  
21 tissue consequences are very different.

22 CHAIRMAN MALMUD: Anyone else wish to  
23 comment? Debbie?

24 MS. GILLEY: Cindy, your example was for  
25 fluorine 18. You were able to give tissue dose enough

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1 to meet the requirements of a medical of 50 Rem?

2 MS. FLANNERY: Yes, there was an  
3 evaluation done by a licensee, and we also did the  
4 evaluation internally, and that potential was there,  
5 that the 50 Rad limit could be exceeded.

6 MS. GILLEY: However you are really  
7 requesting for therapeutic application, because  
8 fluorine-18 is a diagnostic -

9 MS. FLANNERY: Right. And as far as the  
10 December 18<sup>th</sup>, discussion, ACMUI did give a  
11 recommendation for NRC to keep its current position  
12 and to not require reporting of infiltrations of  
13 diagnostic administrations as medical events even if  
14 that 50 rad was exceeded.

15 We think the question that is really on  
16 the table right now for ACMUI is applicability to  
17 therapeutic administrations. So if ACMUI had a  
18 recommendation on whether that should be considered  
19 for infiltrations of therapeutics.

20 CHAIRMAN MALMUD: Dr. Nag.

21 DR. NAG: We have had in injection of  
22 therapeutic, liquid radioisotope, for many many years,  
23 even when I started my residency, even in the `70s we  
24 were injecting things. So injection of therapeutic is  
25 not new. My feeling is that that we need to restate

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1 our previous position in the December 18<sup>th</sup> 2008  
2 meeting that accepted that it would not be considered  
3 a medical event. We always take the best precaution  
4 we can, as Dr. Eggli had stated. But the 50  
5 centigrade really it is very difficult to apply,  
6 because it depends on the volume that you are  
7 considering. If you take a very small segment of the  
8 stint. That portion will get 50 centigrade even if you  
9 exhibit a very small amount of radioactivity. The 50  
10 centigrade, in almost every circumstance, it will be  
11 exceeded depending on what volume you are considering  
12 at 50 centigrade.

13 CHAIRMAN MALMUD: Dr. Vetter.

14 VICE CHAIRMAN VETTER: Yes, that gets to  
15 something I was thinking too: how would you define  
16 infiltration in this sense, and how would a  
17 technologist recognize that infiltration had occurred?

18 CHAIRMAN MALMUD: That's part of the  
19 question we are being asked. Dr. Eggli?

20 DR. EGGLI: I think there is a partial  
21 position that might be reasonable, which is, if a  
22 therapeutic extravazation results in clinically  
23 obvious tissue damage, then maybe it becomes a medical  
24 event, that first of all if there was no extravazation  
25 there wouldn't have been local tissue damage. And if

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1 there wasn't tissue damage it's probably not of real  
2 interest. So whether the possibilities would be to  
3 consider the criteria of tissue damage resulting.

4 This is one of the things that we actually  
5 worry about very often in diagnostic radiology but we  
6 extravagate nonradioactive iodinated contrast  
7 materials there is actually probably a greater risk of  
8 tissue damage in that arena than anything we are going  
9 to do therapeutically, certainly by volume of cases.

10 But if you wanted to track something I  
11 certainly would track anything that fell short of  
12 actually producing tissue injury.

13 CHAIRMAN MALMUD: I have a question. Has  
14 the - has anyone reported to the NRC an incident of  
15 tissue damage from a therapeutic injection of a  
16 radiopharmaceutical?

17 MS. FLANNERY: Not that I am aware of.  
18 However there was a very recent report that was made  
19 of an infiltration of iodine-125 monoclonal antibodies.  
20 The patient support was not located properly, and so  
21 that is an example of I think an infusion that still  
22 an infiltration had occurred.

23 In this case there was an estimated skin  
24 dose of 360 to 710 rads, but there were no adverse  
25 effects seen at the injection site.

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1 CHAIRMAN MALMUD: No visual evidence of  
2 tissue damage was reported. Thank you.

3 Someone? Steve?

4 MR. MATTMULLER: I guess I would like to  
5 add on to Dr. Eggli's remark. I guess the first  
6 question that comes to mind, how would you know?  
7 Because after most therapeutic infusions, we don't  
8 scan. So unless there is obvious tissue damage  
9 afterwards we would never know.

10 CHAIRMAN MALMUD: It may become an issue  
11 in the future. I'm old enough to remember the  
12 earliest days of chemotherapy when the infiltration of  
13 a chemotherapeutic agent intravenously,  
14 nonradioactive, would result in tissue damage. And at  
15 that time the hospital that I was training in hired a  
16 nurse whose sole responsibility was the injection -  
17 preparation and injection of the chemotherapeutic  
18 agents so that they wouldn't be in the hands of  
19 everyone else who was doing IVs. But I'm not aware of  
20 anything that has occurred as yet with a  
21 radiopharmaceutical.

22 Dr. Howe?

23 DR. HOWE: I don't have an example of  
24 that, but just to answer an earlier question, and that  
25 would be, if we were to go in this direction, what

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1 kind of criteria would we use? We don't use the word,  
2 diagnostic, and therapeutic, very often. And so I  
3 would think we would make the distinction between  
4 written directive and non-written directive.

5 That would eliminate the 30 microcuries of  
6 I-131, because that is oral. And we are talking about  
7 something that is being injected.

8 So you would be in essentially for all  
9 practical purposes your therapeutic administrations.  
10 And then if as Dr. Eggli said you wanted to go to  
11 obvious tissue damage then that limits the number  
12 further to effects. And to answer your question about  
13 the future, as we get into more beta pharmaceuticals  
14 we have a higher potential.

15 CHAIRMAN MALMUD: Yes. Dr. Welsh.

16 DR. WELSH: So I would say I like Dr.  
17 Eggli's comment because if we need to do anything at  
18 all. Because if we want to say that we are going to  
19 go with the dose, more than 50 centigrade and 50 rem,  
20 first of all how do you verify the dose? And  
21 secondly, as Dr. Nag pointed out, there are area and  
22 volume concerns here, so that a small microscopic area  
23 might get 50 Rem. Other square centimeters might get  
24 less than that.

25 So it becomes a very tricky analysis.

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1 Therefore if we are going to do anything at all I  
2 would favor what Dr. Eggli said, that the important  
3 point is if there is any tissue damage, that's the  
4 important criteria.

5 CHAIRMAN MALMUD: Dr. Nag.

6 DR. NAG: If you go by tissue damage, the  
7 tissue damage can be called both by the extravazation  
8 of the radioactive material or by the saline or  
9 whatever material that you are giving before or  
10 afterwards. And it becomes difficult to say that this  
11 was - number one it becomes difficult to say what  
12 caused the damage; and number two, the damage  
13 sometimes is caused way later, so you have to come  
14 back and find it late in the day.

15 CHAIRMAN MALMUD: Dr. Eggli.

16 DR. EGGLI: I'm not aware of any case of  
17 saline extravazation causing tissue damage. As a  
18 matter of fact, when you can't get an IV  
19 administration of saline to a vastly dehydrated  
20 patient interstitially is an accepted practice. So  
21 again I'm not aware of the vehicle for a radioactive  
22 treatment having the capability of being responsible  
23 for tissue damage.

24 CHAIRMAN MALMUD: I think you are correct  
25 with regard to the saline. You perhaps, Dr. Nag,

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1 meant the pharmaceutical itself rather than the  
2 radioactive component of it causing the irritation and  
3 the tissue damage.

4 Dr. Howe pointed out an interesting  
5 element, and that is that the way we might describe  
6 this is with a written directive rather than  
7 therapeutic dose. The question is, should this be  
8 just reported as a non-event but at least reported for  
9 recordkeeping. Or is this something that really is  
10 already handled with regard to the individual  
11 institution or lab or office that injected the  
12 pharmaceutical, radiopharmaceutical, having to deal  
13 with sequellae of a local reaction? Which is what can  
14 happen on a regular basis in other situations. These  
15 things occur without radioactivity in the hospital,  
16 and the patients are certainly quite eloquent in  
17 pointing out the pain or the irritation that has  
18 occurred, and the hospital does have to deal with  
19 these issues directly. I'm not sure I have an answer.

20 Ralph.

21 MR. LIETO: If we have then reported,  
22 then what are you going to do with the data? I mean  
23 are you going to - I mean in terms of like a remedial  
24 action or a root cause, I mean I'm really at a loss as  
25 to you are reporting this data, but what are you going

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1 to do with it if you have them report this? And I  
2 think you are looking at such an extremely unusual  
3 occurrence. If this was happening more often, I would  
4 have thought we would hear about this as occurring  
5 with licensees. Which I have a question, the report  
6 that you have with the monoclonal antibodies, was this  
7 something that was in the literature? Was this  
8 something just reported to a region? Or -

9 MS. FLANNERY: It happened in an  
10 Agreement State, like it was just reported two weeks  
11 ago.

12 MR. LIETO: Okay, so this was like an  
13 event report?

14 CHAIRMAN MALMUD: It may be that we  
15 should - oh, go ahead.

16 MR. LIETO: Because you know a question  
17 regarding the dose, which I think either Dr. Vetter or  
18 someone talked about, is the methodology that they are  
19 using to calculate these doses I think needs to be  
20 reviewed, because looking at the - with the fluorine-  
21 18 I mean it's kind of like, okay, you pick the size,  
22 and then this is the dose that you will get. And then  
23 they range from above reporting to below reporting.

24 So I think if we are going to do some type  
25 of dose assessment on this, I think there needs to be

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1 standardization on the dosimetry and how we are going  
2 to calculate this.

3 CHAIRMAN MALMUD: And certainly part of  
4 the issue will be separating the reaction to the  
5 radioactivity versus the reaction to the  
6 pharmaceutical. And we don't have any database or  
7 expertise for handling that. Also, the issue hasn't  
8 occurred yet, so we are talking about a theoretical  
9 issue at the moment.

10 Dr. Suleiman and then Dr. Nag I think.

11 DR. SULEIMAN: Something like this should  
12 be reported to FDA under their adverse event or severe  
13 adverse event reporting system. If it's a  
14 pharmaceutical that causes some severe problems, it  
15 would get - it should get reported. It could be that  
16 there is misinformation on the labeling in terms of  
17 how it's used. It could be the medical device through  
18 which it is being administered.

19 So there are also - the nonradioactive  
20 risk components of the whole process. So there are  
21 mechanisms to get this reported. So if we see a trend  
22 with a specific drug, or if we see a trend with a  
23 specific medical device we will take action.

24 CHAIRMAN MALMUD: Then we will hope that  
25 Dr. Suleiman's agency will inform us at the

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1 appropriate time if necessary.

2 Dr. Nag.

3 DR. NAG: I would highly support Dr.  
4 Suleiman's suggestion that this is already being  
5 reported as an adverse event. However the first thing  
6 before us is, should NRC consider it as a medical  
7 event. Now if we consider this as a medical event, if  
8 we go through all the procedures and identify  
9 whatever-3 or 4 or 5-- the patient will have to be  
10 informed; the physician have to be informed, blah blah  
11 blah, and the - you have to go into all the reporting  
12 mechanisms. And therefore I am thoroughly against  
13 this being reported as a medical event.

14 CHAIRMAN MALMUD: Would you make a motion  
15 that this not be reported as a medical event at the  
16 current time?

17 DR. NAG: Yes.

18 CHAIRMAN MALMUD: Second to your motion?

19 Dr. Welsh seconds the motion.

20 Is there any further discussion of this  
21 motion? Dr. Eggli?

22 DR. EGGLE: Just one residual comment.  
23 If I were to use residual damage, I would put  
24 permanent in front of it. And I'll tell you what, the  
25 patient already knows. So there are no reporting

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1 issues.

2 But that doesn't mean I disagree with the  
3 motion that Subir is making.

4 CHAIRMAN MALMUD: You wish to amend the  
5 motion to have the word, permanent -

6 DR. EGGLI: Well, no, right now Subir's  
7 motion is that therapeutic infiltrations not be  
8 considered medical events. But regardless if there is  
9 permanent tissue damage, the patient knows; the  
10 referring doctor knows; and everybody knows.

11 CHAIRMAN MALMUD: And it would go through  
12 the FDA probably.

13 So the motion is not amended. It has been  
14 seconded. Any further discussion of the motion? Yes.

15 DR. FISHER: Just a quick question. It  
16 may not be a medical event. Is it still a  
17 misadministration in your view?

18 DR. NAG: The word, medical event, has  
19 replaced mis-administration. So mis-administration  
20 and medical event are now synonymous. We don't use  
21 the word, mis-administration, anymore.

22 DR. FISHER: That's why I asked the  
23 question, because does the intended  
24 radiopharmaceutical provide any benefit to the  
25 patient? Was there enough material that - I mean

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1 maybe you had skin damage at the point of injection.  
2 Did the patient still receive the intended benefit of  
3 the infusion? Or was it a mis-administration that  
4 resulted in the patient not receiving the desired  
5 treatment?

6 DR. NAG: There is a technical definition  
7 of medical event, and it is very specific. For  
8 example in a permanent implant you administer the  
9 required number of millicuries. It went to the proper  
10 place, but then migrated to other areas. That is not  
11 called a medical event. It is not what we intended,  
12 but that is not a medical event.

13 I think this is something very similar.

14 CHAIRMAN MALMUD: Excuse me, Dr. Nag,  
15 what Dr. Fisher is saying, if I may interpret it, is  
16 that if you intended - if the intention was to  
17 administer 10 millicuries, but 8 millicuries  
18 infiltrated at the injection site, and the patient  
19 only was able to get two millicuries intravenously to  
20 the target organ, since he only got 20 percent of the  
21 administered dose was that - isn't that a medical  
22 event? That's what Dr. Fisher meant by his question  
23 if I interpreted his question correctly. Then Dr.  
24 Eggli, you had a comment.

25 DR. EGGLI: I think in response to

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1 Darrell on this, the answer is by the definition of  
2 medical event, yes, it's a medical event. However  
3 this particular medical event is specifically exempted  
4 from being defined as a medical event. If that sounds  
5 circular, but this occurrence would meet the medical  
6 event criteria, but it is specifically exempted from  
7 consideration as a medical event.

8 CHAIRMAN MALMUD: What exempts it from  
9 consideration?

10 DR. EGGI: Infiltration. It is  
11 specifically exempted from being defined - by  
12 definition the medical event, the infiltration is  
13 exempted from being classified as a medical event.

14 MS. FLANNERY: That is correct. Based  
15 on the statement and the supplementary information.

16 CHAIRMAN MALMUD: Thank you.

17 Mr. Lieto?

18 MR. LIETO: I'm going to be maybe on thin  
19 ice by disagreeing with Dr. Eggi, but I would not  
20 consider it a medical event. Because not based on the  
21 exemption; it's because the written directive was to  
22 administer 10 millicuries. They administered 10  
23 millicuries. The written directive isn't a 10  
24 millicuries - that so many millicuries goes to a  
25 certain organ, so forth and so on. So if they

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1 administer 10 millicuries -

2 DR. EGGLI: I have to disagree -

3 CHAIRMAN MALMUD: You are both agreeing  
4 though that it is not a medical event.

5 DR. EGGLI: But I have to disagree with  
6 Ralph because part of the written directive specifies  
7 route of administration.

8 CHAIRMAN MALMUD: And Flannery has  
9 explained the reg, and the reg speaks for itself; so  
10 we will live with the reg as it is. And it still is  
11 in line with the motion on the floor.

12 Have we voted on the motion?

13 DR. NAG: Not yet.

14 CHAIRMAN MALMUD: No. May we vote on the  
15 motion? Want to call the motion?

16 All in favor?

17 (Show of hands.)

18 CHAIRMAN MALMUD: Any opposed?

19 (Show of hands.)

20 CHAIRMAN MALMUD: Any abstentions?

21 (Show of hands.)

22 CHAIRMAN MALMUD: One abstention - oh  
23 excuse me, two abstentions. So the motion passes.  
24 Thank you.

25 MS. FLANNERY: All right, thank you very

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1 much.

2 CHAIRMAN MALMUD: Thank you.

3 We will now move ahead, and the next item  
4 is the summary of the enforcement process and  
5 enforcement actions against medical licensees.

6 MS. COCKERHAM: Dr. Malmud, can I suggest  
7 that we take a break, and then we will resume with the  
8 outgoing member presentations?

9 CHAIRMAN MALMUD: Yes, we will. We will  
10 follow your suggestion. Thank you.

11 (Whereupon, the above-entitled matter went off the  
12 record at 2:36 p.m. and resumed at 2:49  
13 p.m.)

14 CHAIRMAN MALMUD: Ashley.

15 MS. COCKERHAM: We can go straight into  
16 outgoing member presentations, if Dr. Nag wants to  
17 start, and then Mr. Lieto, followed by Dr. Vetter.

18 CHAIRMAN MALMUD: All right, thank you.  
19 We now invite our outgoing members to give a  
20 presentation, if they wish, beginning with Dr. Nag.

21 DR. NAG: I am not going to make any  
22 formal presentations. I know everybody is waiting to  
23 -- would like to finish this off very quickly. But I  
24 would really like to thank and appreciate all the NRC  
25 officials, all the current as well as the past ACMUI

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