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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

Submitter Information

Name: Robert Van Arnam
Address:
300 Fayetteville Street
Raleigh, NC, 27607
Email: rvanarnam@williamsmullen.com

General Comment

Commissioners - Please see the attached letter and exhibits

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to you and particularly to your general counsel on behalf of the Petition (Docket ID NRC-2020-0141) and ask that the outdated reporting exemption be lifted.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.

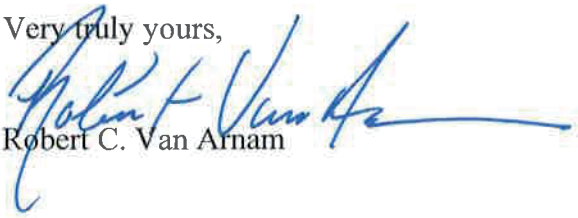
Third, and most significantly, extravasations are not benign. The opponents, including the HPS, state in opposition that: "there is no evidence that infiltration of radiopharmaceuticals carries **any** health consequences for the patient or the general public" (emphasis added). That statement is verifiably 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.

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

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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 Quaity for 18F-FDG, 68Ga-PSMA and 68Ga-DOTATATE Positron Emission Tomography. J of Medical Imaging and Radiation Sciences, 2020. **51**: p. 247-255.
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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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I realize that you have to take time out of your busy schedules to do those. But the management of NRC is held very accountable to making sure everyone has jumped through all the hoops on all of those periodic training requirements.

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

CHAIRMAN MALMUD: Are there any questions? This is Malmud. Are there any questions?

(No response.)

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

CHAIRMAN MALMUD: Thank you. We have the next item on the agenda, which will be Cindy Flannery. Am I correct, Cindy?

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

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

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

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

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

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

radiation injury.

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

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

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

extravasation to be a misadministration."

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

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

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

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

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

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

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

So that concludes my opening of the discussion.

CHAIRMAN MALMUD: Thank you, Cindy.

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

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

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

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

CHAIRMAN MALMUD: Dr. Vetter?

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

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

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

CHAIRMAN MALMUD: Thank you.

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

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

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

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

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

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

radiopharmaceuticals.

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

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

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

CHAIRMAN MALMUD: Thank you, Dr. Nag.

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

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

CHAIRMAN MALMUD: Thank you.

Dr. Nag, are you seconding that motion?

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

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

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

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

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

supplementary information.

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

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

CHAIRMAN MALMUD: Thank you. Dr. Eggli?

MEMBER EGGLI: There are -- infiltrations just always occur. If they were to become medical events, the NRC would be flooded with more medical events than it could manage. But, in addition, the radiation is a function of the volume of distribution. Obviously, the smaller the volume of the infiltration the higher the local radiation dose. In 30 years of clinical practice, I have seen lots and lots and lots of infiltrations. I have never seen an adverse clinical outcome.

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

CHAIRMAN MALMUD: Thank you, Dr. Eggli. I

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

Are there other comments or discussions regarding the motion?

MEMBER LIETO: This is Ralph Lieto.

CHAIRMAN MALMUD: Yes, Mr. Lieto.

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

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

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

MEMBER LIETO: Yes, because it basically reaffirms that.

CHAIRMAN MALMUD: Thank you.

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

CHAIRMAN MALMUD: Please do.

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

MEMBER LIETO: I accept that clarification.

CHAIRMAN MALMUD: Thank you, Mr. Lieto.

Any other discussion of the motion on the floor?

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

But in these cases, as was mentioned by

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

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

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

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

MEMBER FISHER: Dr. Malmud?

CHAIRMAN MALMUD: Yes. Who is speaking, please?

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

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

CHAIRMAN MALMUD: Are you asking me specifically?

MEMBER FISHER: Yes. And Dr. Eggli.

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

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

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

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

theoretical possibility that we will see some untoward effect from an infiltration of a therapeutic dose. However, I cannot personally speak to that experience. Perhaps Dr. Eggli may.

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

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

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

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

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

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

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

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

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

medical event.

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

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

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

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

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

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

Are there any other comments regarding the diagnostic?

(No response.)

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

(Chorus of ayes.)

Are there any opposed to the motion?

(No response.)

Are there any abstentions?

(No response.)

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

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

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

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

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

MEMBER LIETO: The regulations do not.

CHAIRMAN MALMUD: Should they?

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

CHAIRMAN MALMUD: Thank you.

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

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

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

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

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

MEMBER NAG: Yes, that is agreeable.

CHAIRMAN MALMUD: Thank you.

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

CHAIRMAN MALMUD: Yes, Cindy.

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

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

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

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

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

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

in a therapeutic infusion is really very small.

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

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

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

MEMBER EGGLI: This is Doug Eggli. I

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

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

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

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

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

its ramifications. Is that acceptable to the committee?

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

MEMBER EGGLI: This is Doug Eggli. I agree.

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

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

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

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

MEMBER SULEIMAN: I agree.

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

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

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

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

If that is acceptable with the committee,

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

(Several members respond in the affirmative.)

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

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

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

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

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

VICE CHAIRMAN VETTER: Okay.

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

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

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

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

CHAIRMAN MALMUD: -- the practice of my

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the patient was scheduled for.

CHAIRMAN MALMUD: Thank you. May we move on?

Thank you very much, Mr. Lieto.

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

MS. FLANNERY: Well, this presentation is really just a continuation of a discussion we had at the December 18th, 2008 teleconference. And I will just briefly summarize that discussion and where we left off.

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

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

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

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

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

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

DR. EGGLI: As a person that does some of

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

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

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

CHAIRMAN MALMUD: Anyone else wish to comment? Debbie?

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

to meet the requirements of a medical of 50 Rem?

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

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

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

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

CHAIRMAN MALMUD: Dr. Nag.

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

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

CHAIRMAN MALMUD: Dr. Vetter.

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

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

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

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

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

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

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

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

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

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

Someone? Steve?

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

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

Dr. Howe?

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

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

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

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

CHAIRMAN MALMUD: Yes. Dr. Welsh.

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

So it becomes a very tricky analysis.

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

CHAIRMAN MALMUD: Dr. Nag.

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

CHAIRMAN MALMUD: Dr. Eggli.

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

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

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

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

Ralph.

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

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

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

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

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

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

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

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

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

Dr. Suleiman and then Dr. Nag I think.

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

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

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

appropriate time if necessary.

Dr. Nag.

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

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

DR. NAG: Yes.

CHAIRMAN MALMUD: Second to your motion? Dr. Welsh seconds the motion.

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

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

issues.

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

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

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

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

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

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

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

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

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

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

I think this is something very similar.

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

DR. EGGLI: I think in response to

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

CHAIRMAN MALMUD: What exempts if from consideration?

DR. EGGLI: Infiltration. It is specifically exempted from being defined - by definition the medical event, the infiltration is exempted from being classified as a medical event.

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

CHAIRMAN MALMUD: Thank you.

Mr. Lieto?

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

administer 10 millicuries -

DR. EGGLI: I have to disagree -

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

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

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

Have we voted on the motion?

DR. NAG: Not yet.

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

All in favor?

(Show of hands.)

CHAIRMAN MALMUD: Any opposed?

(Show of hands.)

CHAIRMAN MALMUD: Any abstentions?

(Show of hands.)

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

MS. FLANNERY: All right, thank you very

much.

CHAIRMAN MALMUD: Thank you.

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

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

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

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

CHAIRMAN MALMUD: Ashley.

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

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

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