

1 MS. BROGDON: That's right.

2 DR. CASTELLINO: Tab 1, page 1.

3 DR. IBBOTT: And this is being presented
4 also in the sponsor's presentation. Are there
5 comments about this? From a physicist's point of view
6 it seems straightforward but perhaps that's not the
7 appropriate -- I'm not the appropriate reader for
8 this. It's the person who would be using the system.

9 DR. SOLOMON: This may be a good place to
10 include the always and never thing that we've been
11 talking about. I don't know if this is the
12 appropriate place.

13 DR. KRUPINSKI: This is also why it would
14 be interesting that we could have seen the difference
15 between the classic and the not classic. Here you're
16 talking more about classic nodules and performance
17 based strictly on those to see if this truly is
18 appropriate.

19 MR. MILLER: Just to clarify quickly, the
20 primary analysis is based on all unanimous nodules.
21 It was one of the sensitivity analyses that --

22 DR. KRUPINSKI: Right, but not all of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 those were classic.

2 MR. MILLER: That's correct.

3 DR. SOLOMON: The only other thing, I
4 guess, is to possibly emphasize the fact that somebody
5 doesn't realize that ground glass nodules would not be
6 included in this. If I just read it kind of casually,
7 it's a solid pulmonary nodule, I might think all
8 nodules would be included, whereas you might want to
9 distinguish the fact that the system is not meant for
10 ground glass nodules or other things.

11 DR. KRUPINSKI: You mentioned satisfaction
12 of search here and I'm just wondering if there is a
13 reverse. You are going through -- there's all these
14 other abnormalities. You note, yeah, there's
15 atelectasis back here. Then you go and you bring up
16 the nodules. Has anybody looked at the possibility
17 that you are going to get a reverse SOS and now you're
18 all concentrated on the nodules and you forget to
19 report the initial findings. Has anybody looked at
20 that?

21 I mean, if you're not going to give your
22 report, you know, if you're not going to sit there and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 dictate before you look at the CAD, there's the
2 possibility that now you're all wrapped up in the CAD
3 and all of a sudden the other stuff goes out of your
4 mind. Clinically do you see that happening?

5 MR. MacMAHON: Well, I haven't actually
6 used this system so I'm just speaking from general
7 experience. Of course, in reading CT scans, as I
8 think Dr. Castellino described, we go through it
9 multiple times already.

10 We go through the mediastinum and
11 personally I make notes, or my resident makes notes as
12 we go through because it's really hard to remember all
13 of the abnormalities in all of the areas so I take a
14 second run or a third run and look for pulmonary
15 nodules and abnormalities and make more notes. My
16 instinct is that it would not be an issue.

17 DR. TRIPURANENI: As I read through this
18 again, I guess now that we have Dr. Stark's comments
19 and others, the second paragraph is an interesting
20 paragraph. I don't want to wordsmith. That is
21 certainly not my expertise.

22 If you look at the first sentence in the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 second paragraph, it kind of vents with the other
2 recognized causes of a suboptimal view. I'm just
3 raising the question. Potentially a radiologist could
4 actually bar the system by looking at the indications.

5 I'm not saying he will. The hole in the whole system
6 there he could actually say, "I can slack off a little
7 bit.

8 The system is going to pick up the nodule
9 there." I think once again always and never are very
10 important to really put it on the face kind of stating
11 it every single time. The whole system is predicated
12 on those two.

13 DR. CONANT: I think there could also be
14 further contraindications in the warnings and
15 precautions. I mean, again, just emphasizing the
16 always and the nevers but I'm not sure you can dictate
17 what people actually do.

18 DR. STARK: But isn't it fair to say that
19 given the combination that they are making a claim
20 here that it relieves you of fatigue and distraction
21 or other recognized causes of suboptimal review. I
22 mean, these are bold statements that are going to be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 used by marketing people to radiologist to look at
2 this.

3 DR. CONANT: Where does it say "relieves?"

4 DR. STARK: I'm sorry. It lapses. I
5 misconstrued it. The chance of observational lapses
6 by the reader due to fatigue. Well, the next patient
7 that the same radiologist read after having to deal
8 with these false positives, one could make an argument
9 there's more risk to the next patient.

10 DR. CONANT: One way to deal with this is
11 basically the second paragraph nobody really likes a
12 lot because who wants to read about our lapses and
13 fatigue, right? Maybe that's not necessary here if
14 always and never is emphasized. Is that happy?

15 DR. STARK: I think if the FDA has our
16 point that we are unhappy with the language, I'll
17 leave it at that.

18 DR. CONANT: We don't like to be called
19 tired and distractable.

20 DR. IBBOTT: Mr. Burns.

21 MR. BURNS: If I remember correctly
22 earlier during your presentation, you indicated this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 algorithm does not work with low dose chest CT.
2 Correct?

3 DR. CASTELLINO: No, I did not. I said
4 that the clinical cases that were collected for the
5 ROC study were all clinically indicated studies. That
6 is, they did not contain any type of screening low-
7 dose exam. In our test database a substantial number
8 of the cases are, in fact, low-dose CT scans and
9 performs quite well in that, or equivalently well in
10 that. But specifically for the ROC study they just
11 happen to be clinically indicated exams like you see
12 in most hospital practices or out-patient practices.

13 MR. BURNS: Okay. So what you have in the
14 warnings regarding the MAS levels covers that issue.
15 Correct?

16 DR. CASTELLINO: Correct.

17 DR. IBBOTT: All right. Then let's move
18 on again to the fourth question. I think we have an
19 indication where we're going on this one, too. If the
20 PMA were to be approved, please discuss whether the
21 above or any other issues not fully addressed in the
22 PMA (A) require post-market surveillance measures in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 addition to the customary medical device reporting.
2 Several people have suggested that they would like to
3 see additional studies done if this device were to be
4 approved. Those of you who have called for that,
5 would you like to elaborate?

6 DR. STARK: Well, I've mentioned --
7 actually seen data. I'm not inclined to argue with
8 the perceptions because I think it's likely correct
9 that low-dose contrast but the public needs to see
10 this. This needs to be written down somewhere so it's
11 objective and hopefully some statistics can be applied
12 to it.

13 Artifacts due to common thoracic
14 interventions such as excision of one of these
15 nodules, a clip left behind, radiation and damage,
16 patients who can't put their arm over their head. I
17 think those are the major things that are medical in
18 nature. I think one of the things -- there needs to
19 be something negotiated with the FDA in terms of
20 minimum.

21 You've got already minimum CAT scan or
22 technology but as CT technology evolves what would

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 trigger a change in surveillance. It may be a
2 different category but under this if this PMA were
3 approved, again, the technical experts at the FDA need
4 to negotiate what is some minimum quantum change in
5 the technology that would require a new PMA and
6 review. Is it going to remain a class three device or
7 what would it be? Is it going to be a 510(k)
8 application of substantial equivalence?

9 Again, I alluded to earlier I don't know
10 what algorithm is used here and I'm not a computer
11 scientist but what is a trivial change to a layman may
12 be very significant to a copyright attorney or a
13 radiologist. If the algorithm switched entirely to
14 being, say, a MIP of subtraction or something like
15 that, at some point there has to be some disclosure
16 and review, I would think, of the performance.

17 DR. O'SHAUGHNESSY: Can I just comment on
18 that last point? They are very well established
19 guidelines that FDA has with manufacturers as to what
20 requires a change. Any change in the product has to
21 be evaluated against certain criteria and then those
22 will be based on the approved labeling. Everything

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 that the panel contributes here today will go into
2 deciding what changes in the product require further
3 review by FDA.

4 DR. STARK: Well, then for the FDA's sake
5 I'm not aware of what those are and they will do
6 diligently well to merge that with some of the
7 insights we have learned today because certainly we've
8 heard a lot of novel things today that are novel to
9 everybody in this room. They are going to be novel to
10 the people that developed those guidelines perhaps
11 with the breast nodule detection in mind but they may
12 not be totally opposite here.

13 DR. CONANT: The things that I raised
14 before just to summarize, and I'm not sure where they
15 fit in preapproval or post-approval because I'm not
16 sure if we made that decision yet but, again, it's a
17 case-based analysis versus multiple nodules,
18 quadrants, all that. You've heard that multiple
19 times. A little more insight based on case-based
20 analysis of false positives and false negatives.

21 I think that's really important. We've
22 been talking a lot about the false positives but I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 think the false negatives are fascinating. What
2 happens when you've got really defuse lung disease?
3 One of the exclusion criteria here was greater than 10
4 nodules. I mean, what about someone who has -- I
5 don't know what disease that would be but a gazillion
6 -- yeah, sarcoid, right. Granulomas everywhere, old
7 TB, whatever. Where can this really be used
8 effectively and where does it really just fall down.

9 Also your cases were over 19 years of age.

10 What happens in the pediatric? You know people are
11 going to start applying this everywhere. That just
12 came to me recently. That has to be included, I
13 guess, in the labeling and certain analyzed. Whether
14 it's pre-post approval, I mean, that's what we're here
15 for.

16 DR. SOLOMON: I would just add the
17 thoughts on making the study more real life so
18 collecting data maybe on the perspective fashion that
19 will essentially test the system in real life
20 conditions. Real-life conditions for the doctor,
21 real-life conditions of diseases and everything, and I
22 guess a real-life test essentially.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. TRIPURANENI: I would recommend the
2 same. I think whether it's pre or post I think there
3 needs to be a follow-up study of the patients that are
4 going to go through this to see what is the clinical
5 impact ultimately.

6 DR. IBBOTT: All right. Well, I think
7 we're on the verge then of deciding if it's going to
8 be a pre or a post-approval study. Unless there are
9 other concerns that you want to address now, I suggest
10 that we move on.

11 We now come to a second half-hour open
12 public hearing session. If there are any individuals
13 wishing to address the panel, please raise your hands
14 and identify yourselves at this time. Seeing none,
15 then we move on.

16 Before we move to the panel
17 recommendations and vote, is there anything additional
18 the FDA would like to address?

19 DR. DOYLE: Now that the panel discussion
20 is over, we would ask the sponsors to go back to their
21 seats, please.

22 DR. WAGNER: Fear not. I will not make a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 technical comment but since Dr. Blumenstein's position
2 is heavily influenced by some of his statistical
3 comments, I would just like to tell you that the issue
4 about correlation across modalities has been addressed
5 in the literature by a number of authors including
6 myself and it's at the bottom of the third page of the
7 references there.

8 Modalities are not a random effect but
9 cases and readers are. The entire correlation
10 structure is accommodated by the model here. Also the
11 sampling scheme does sample the intra-reader
12 variability, as I said this morning. Two out of three
13 of your points are, in fact, addressed in the
14 literature. Thank you.

15 DR. IBBOTT: And, finally, is there
16 anything else the sponsor would like to address?

17 DR. O'SHAUGHNESSY: No, thank you. We
18 appreciate the questions very much.

19 DR. IBBOTT: Thank you.

20 DR. DOYLE: All right. We will now move
21 to the panel's recommendations concerning PMA P030012.
22 The Medical Device Amendments to the Federal Food,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Drug, and Cosmetic Act (the Act) as amended by the
2 Safe Medical Devices Act of 1990, allows the Food and
3 Drug Administration to obtain recommendation from an
4 expert advisory panel on designated medical device
5 premarket approval applications, PMAs, that are filed
6 with the agency.

7 The PMA must stand on its own merits and
8 your recommendation must be supported by safety and
9 effectiveness data in the application or by applicably
10 publicly available information. Safety is defined in
11 the Act as reasonable assurance based on valid
12 scientific evidence that the probable benefits to
13 health under conditions of intended use outweigh any
14 probable risks.

15 Effectiveness is defined as reasonable
16 assurance that in a significant portion of the
17 population, the use of the device for its intended
18 uses and conditions of use when labeled will provide
19 clinically significant results.

20 Your recommendation options for the vote
21 are as follows: Approvable if there are no conditions
22 attached. Approvable with conditions. The panel may

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 recommend that the PMA be found approvable subject to
2 specified conditions such as physician or patient
3 education, labeling changes, or further analysis of
4 existing data. Prior to voting all the conditions
5 should be discussed by the panel.

6 Finally, not approvable. The panel may
7 recommend the PMA is not approvable if the data do not
8 provide reasonable assurance that the device is safe
9 or if a reasonable assurance has not been given that
10 the device is effective under the conditions of use
11 prescribed, recommended, or suggested in the proposed
12 labeling. If the vote is for not approvable, the
13 panel should indicate what steps the sponsor may take
14 to make the device approvable.

15 DR. IBBOTT: All right.

16 DR. TRIPURANENI: May I ask you to read
17 the effectiveness statement again please? I want to
18 listen to it again.

19 DR. DOYLE: I would be happy to do that.
20 Effectiveness is defined as reasonable assurance that
21 in a significant portion of the population, the use of
22 the device for its intended uses and conditions of use

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 when labeled will provide clinically significant
2 results.

3 DR. TRIPURANENI: Thank you.

4 DR. IBBOTT: Would anyone on the panel
5 care to make a motion?

6 DR. BLUMENSTEIN: I move "not approvable."

7 DR. IBBOTT: It's been moved not
8 approvable. Is there a second to this motion?

9 DR. STARK: I'll offer a second.

10 DR. IBBOTT: I'm sorry?

11 DR. STARK: I would offer a second.

12 DR. IBBOTT: All right. It's been moved
13 and seconded. Is there discussion then of this
14 motion?

15 DR. KRUPINSKI: Can we discuss the
16 procedure? Do we discuss it --

17 DR. STARK: And then vote.

18 DR. IBBOTT: And then we will vote.

19 DR. KRUPINSKI: On that motion?

20 DR. IBBOTT: On this motion.

21 DR. KRUPINSKI: And then it takes two-
22 thirds to --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. STARK: Majority.

2 DR. KRUPINSKI: Majority.

3 DR. STARK: If that motion doesn't pass,
4 then we'll ask for another motion.

5 DR. CONANT: I'll say something. I think
6 there is a lot of very rich data here. There's more
7 data we'd like, of course, that they don't have like
8 follow-up studies to your follow-ups. You know, what
9 happened to the patients. But within the data that
10 they've given us, I'm sure they can look at it by case
11 and look at false positives, even false negatives.

12 I would hesitate to jump yet to not
13 approvable without at least getting that data that
14 should be obtainable without IRBs and all that stuff
15 because you guys should have it on those spreadsheets
16 by patient and have a second look at that. That's
17 where I stand with the non-approvable part.

18 DR. SOLOMON: I agree with what you just
19 said. I mean, I think we're put in a difficult
20 position here. I think all of us seem to be asking
21 for more clinically relevant case data. It seems like
22 something you might have but we don't have that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 information right now. That's difficult when the
2 statement for efficacy says clinically significant
3 results and it's hard for us without having
4 necessarily those clinically relevant information. I
5 think that pretty much sums up the issue right there.

6 DR. TRIPURANENI: As a clinician we have
7 high-tech in radiation therapy using lots of machines
8 and equipment to follow-up things right in there.
9 Having practiced for more than 20 years, I have come
10 to believe that any process you improve typically
11 improves the patient outcomes. Sometimes I believe
12 it's a leap of faith but I think most of the things
13 that you do in the clinic that you improve usually
14 improves the outcome.

15 I would like to believe that actually the
16 fact that you can actually pick up a few more modules
17 I think eventually will translate into some sort of
18 positive impact on patient management. I really would
19 love to see some data. In fact, that's where I have
20 the dilemma. I asked Mr. Doyle to repeat the
21 effectiveness statement right there.

22 I think if you follow the rule of the law

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 right there, I have to make a real leap of faith that
2 actually this is improvement. My personal belief is
3 that any improvement in the process will improve the
4 care so I have to really make the leap of faith to
5 actually work for it but I think it's a dilemma, as
6 Dr. Solomon said, that we're all in. I really would
7 love to see some clinical data.

8 DR. KRUPINSKI: Just to be specific, I
9 think what we're after is on a patient basis how many
10 normals were then converted to a false positive to
11 abnormal and then how many false negative patients and
12 back and forth on each one. I mean, all possible
13 combinations. I think that is specifically what we're
14 looking for.

15 DR. STARK: If I could offer another
16 analogy, a brief one.

17 DR. IBBOTT: Are you addressing the
18 motion?

19 DR. STARK: Yes, I think so. I'll be
20 brief. The issue of approving gadolinium DTPA for MR
21 scanning of the brain was obvious, as it is here, as
22 we've heard from statisticians and clinicians. Given

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the constraints of this study it's really obvious to
2 us that this technology likely makes things better.
3 But unlike the decision to approve gadolinium at a
4 cost of billions of dollars because we saw a few
5 anecdotes where it made things better, no one had an
6 argument that it could make things worse or make
7 things less efficient. Here there are serious
8 concerns that the marginal improvement in efficacy
9 which is perhaps buried in the statistics is offset by
10 a much more obvious risk to the patients here.
11 Forgive me if that's not on the point of the motion
12 but I think the panel has done a lot of soul searching
13 and that's the reason why I think we have hesitated --
14 my hesitation.

15 DR. IBBOTT: It seems to me that this
16 device provides information that is not available
17 otherwise and more information is usually better. I
18 share your concern to some extent. Certainly not to
19 the degree that you do, I think, though, that people
20 may misuse the device or take advantage of it to relax
21 in their own vigilance. I think the sponsor can
22 address that.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Yes, Dr. Ferguson.

2 DR. FERGUSON: It seems to me that the
3 company has followed very carefully the suggestions of
4 the FDA and I applaud them for that. I don't think
5 that we should necessarily penalize them for that
6 unless that's the will of the group here because we
7 are advisers only to the FDA. I would side with those
8 who think that more information is required and I
9 think it's been outlined very, very well what that
10 information should be but I don't think -- I would not
11 vote for nonapprovable.

12 DR. IBBOTT: Is there anymore discussion
13 before we prepare for a vote?

14 MS. BROGDON: Dr. Mehta?

15 DR. MEHTA: Yes, I'm here. I can hear the
16 conversation.

17 MS. BROGDON: Do you have a comment?

18 DR. MEHTA: No, actually I don't have
19 anything to add at this point.

20 DR. IBBOTT: All right. Well, in that
21 case we will proceed to the vote.

22 MS. BROGDON: Dr. Mehta can vote if he

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 wishes.

2 DR. MEHTA: Actually, I'm uncomfortable
3 voting because quite a bit of the time it was breaking
4 up and I feel it would do an injustice to the sponsor
5 for me to vote if I've not heard everything clearly.

6 DR. IBBOTT: All right. Fair enough.

7 DR. SOLOMON: Can I ask one question? As
8 far as the categories go if the nonapprovable and the
9 approvable with conditions, where would going back to
10 your data and coming up with some of this clinical
11 evidence that we're asking for fall into?

12 DR. IBBOTT: Well, at the moment we are
13 voting on a motion to declare this application not
14 approvable. If that motion passes, then that's the
15 end of the discussion here.

16 DR. DOYLE: But I think Dr. Solomon's
17 question is where would reanalysis of existing data?

18 DR. STARK: Yes, that was the question
19 based on your definition.

20 DR. DOYLE: That could be part of
21 approvable with conditions. That comes under that
22 definition.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. STARK: Would non-approvable also
2 invite the manufacturer to resubmit answering the same
3 questions? This doesn't go away forever.

4 DR. DOYLE: No. In fact, if that were the
5 case, we would ask each one of you to recommend what
6 you think the sponsor should do to make the advice
7 approvable.

8 DR. MOORE: Can I make a point? I would
9 also second Dr. Conant's point that I think a lot of
10 the data that's being asked by the panel is in the
11 data that the sponsor has available. I think that
12 really should be taken into consideration.

13 Particularly if we're thinking about additional
14 studies here whether it be post-market or pre-market.
15 Obviously if it was non-approvable that would be pre-
16 market. We really need to think about the
17 reasonableness and what it would take for a sponsor to
18 do that.

19 I think the companies worked very well
20 with FDA in trying to identify what is appropriate. I
21 think it's not only FDA that's kind of worked on that
22 but sort of the industry of what's appropriate for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 evaluating this. I think that needs to be taken into
2 consideration.

3 DR. IBBOTT: All right. We will proceed
4 to the vote then and I'll remind you that the motion
5 is not approvable. I'll ask you to state whether you
6 vote yes which means that you are in favor of
7 declaring not approvable, or no in which case you
8 disagree with the motion and would consider a
9 different motion, or abstain. We note that Dr. Mehta
10 has abstained. Dr. Krupinski, I would like to start
11 with you.

12 DR. KRUPINSKI: No.

13 DR. IBBOTT: No. Thank you. Dr. Conant.

14 DR. CONANT: No.

15 DR. IBBOTT: Thank you.

16 DR. FERGUSON: No.

17 DR. IBBOTT: Dr. Solomon.

18 DR. SOLOMON: No.

19 DR. IBBOTT: Dr. Blumenstein.

20 DR. BLUMENSTEIN: Yes.

21 DR. IBBOTT: Dr. Tripuraneni.

22 DR. TRIPURANENI: No.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: Dr. Start.

2 DR. STARK: Yes.

3 DR. IBBOTT: All right. Well, we have two
4 in favor, five opposed, and one abstention. This
5 motion does not carry. We now come back to
6 entertaining another motion. I would like to ask if
7 someone on the panel would like to make a motion.

8 DR. KRUPINSKI: Approve with conditions.

9 DR. IBBOTT: The motion is approve with
10 conditions. Is there a second?

11 DR. FERGUSON: Second.

12 DR. IBBOTT: Dr. Ferguson. Now, we've had
13 quite a bit of discussion but perhaps other Dr.
14 Krupinski or Dr. Ferguson would like to speak to the
15 motion. I'm sorry. The next step is to establish the
16 conditions.

17 DR. KRUPINSKI: One at a time?

18 DR. IBBOTT: One at a time, yes.

19 DR. KRUPINSKI: One condition would be for
20 the post-analysis of the by-patient data

21 DR. IBBOTT: And each condition requires a
22 second.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. CONANT: Second.

2 DR. IBBOTT: Dr. Conant seconded. Now, is
3 there discussion about this condition that would be
4 attached to a motion to approve with conditions?

5 DR. STARK: My question is does the motion
6 imply or should we specify that we are saying that's a
7 condition where the FDA must be satisfied before the
8 product is permitted to be marketed?

9 DR. IBBOTT: That is the meaning of
10 conditions, that it is approvable once the conditions
11 are satisfied.

12 DR. STARK: Okay. And approvable means it
13 would be subject to FDA approval?

14 DR. IBBOTT: That's right. We're making a
15 recommendation to the FDA which they then consider.

16 DR. TRIPURANENI: Dr. Krupinski, could you
17 elaborate the condition? I didn't understand. I'm
18 sorry.

19 DR. KRUPINSKI: Basically what we want
20 instead of the ROC analysis based on the quadrants is
21 to say, okay, here is a patient who is classified as
22 normal. How many times did the radiologist call that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 normal and then because of the CAD called it false
2 positive. And vice versa where they initially called
3 it false positive did the CAD make them now call it
4 true negative.

5 Then how many patients no matter how many
6 nodules they had radiologist says false negative, the
7 CAD correctly turns them to true positive. And vice
8 versa how many times did the radiologist call it true
9 positive and the CAD made them reverse their patient
10 decision and call it false negative.

11 DR. TRIPURANENI: Are you asking for a
12 post-marketing analysis or a pre-market analysis?

13 DR. KRUPINSKI: No, re-analysis of the
14 existing data.

15 DR. TRIPURANENI: Okay. Thank you.

16 DR. STARK: Is it also implied that the
17 FDA -- that's a specific question but I think it is
18 implied -- I'm asking is that implied that is to --
19 certainly not to the exclusion, I would think, of the
20 many other questions the FDA might have based on our
21 discussion today, or should we add our own conditions
22 and try to broaden that? I think so many things have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 been raised here today.

2 I'm so impressed personally with the
3 qualifications of the FDA staff, the clinical staff,
4 Dr. Sacks, the statisticians, that I would want to
5 give them broad discretion and encourage them, in
6 fact, insist that in addition to answering your
7 question that they address many of the other issues
8 that they will see fit to recognize in the transcripts
9 of this proceeding.

10 DR. KRUPINSKI: I'm not sure how broad
11 each division has to be.

12 DR. DOYLE: There's no requirement either
13 way. Keep in mind that the FDA will interpret these
14 conditions so that you can state them in broad terms
15 and we certainly will work with the sponsor to refine
16 them to specific actions. You don't have to spend a
17 lot of time wordsmithing these conditions is what I'm
18 basically saying.

19 DR. IBBOTT: Dr. Blumenstein.

20 DR. BLUMENSTEIN: Let me have
21 clarification here. Are we talking about conditions
22 prior to approval or post-approval conditions? I'm a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 little confused about that.

2 DR. IBBOTT: These are conditions prior to
3 approval.

4 Yes, Nancy.

5 MS. BROGDON: If you have post-approval
6 conditions you want to include here, then you should.

7 DR. IBBOTT: Thank you.

8 DR. KRUPINSKI: So those would be like
9 follow-up on new patients. That would be a post-
10 approval?

11 DR. IBBOTT: A post-approval for condition
12 for approval.

13 MS. BROGDON: I'm sorry. I didn't
14 understand your question.

15 DR. IBBOTT: If we impose conditions that
16 cannot be met until after the device is marketed, then
17 how can that be a condition for approval? Or is it a
18 recommendation at that point?

19 MS. BROGDON: These are all
20 recommendations. If some of them are about post-
21 approval data, then just identify them as such and
22 we'll know how to sort them out.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: Thank you.

2 MS. BROGDON: If you have things that you
3 are specifically looking for, you ought to name them
4 in your conditions.

5 DR. IBBOTT: Good.

6 DR. CONANT: I think things that are pre-
7 approval conditions before we get to post-approval.

8 DR. IBBOTT: Let's deal with them one at a
9 time.

10 DR. DOYLE: Let's try and deal with this
11 one condition.

12 DR. IBBOTT: By the way, we need to vote
13 on each condition so before you --

14 DR. CONANT: I seconded hers, didn't I?

15 DR. IBBOTT: Yes. And are you speaking to
16 that condition?

17 DR. CONANT: No.

18 DR. IBBOTT: Let's vote to make sure we're
19 in agreement to attach this condition and then we'll
20 come back and add more conditions. Is there any other
21 discussion about this condition? Then let's ask Dr.
22 Mehta again if he wishes to vote on these conditions.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 MS. BROGDON: Dr. Mehta, do you wish to
2 vote on any of the conditions?

3 DR. MEHTA: I think I'm going to abstain
4 on that as well.

5 DR. IBBOTT: All right.

6 Dr. Krupinski.

7 DR. SOLOMON: The only other thing on her
8 condition is to -- I mean, it was a very broad
9 statement. Obviously the implication is that the
10 statistics remain favorable on the case analysis. I
11 mean, it's implied.

12 DR. IBBOTT: Good point. Yes.

13 DR. KRUPINSKI: Yes.

14 DR. IBBOTT: Thank you. Dr. Conant.

15 DR. CONANT: Yes.

16 DR. FERGUSON: Yes.

17 DR. SOLOMON: Yes.

18 DR. BLUMENSTEIN: Yes.

19 DR. TRIPURANENI: Yes.

20 DR. STARK: Yes.

21 DR. IBBOTT: All right. Unanimously in
22 favor of that condition.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Now, at this point, Dr. Conant, you could
2 introduce another condition.

3 DR. CONANT: Always and never. Labeling
4 issues. I thin everybody agrees on that to clarify
5 the labeling addressing the many issues we did.

6 DR. IBBOTT: Is there a second?

7 DR. KRUPINSKI: Second.

8 DR. IBBOTT: It's been seconded. Do you
9 want to elaborate on just how you would like them to
10 do that?

11 DR. CONANT: Nobody really liked the
12 second paragraph about fatigue and lapses and to
13 really emphasize this always and never and to have the
14 radiologist be ethical and moral and all those good
15 things. And to really downplay the issues of
16 statistical significance, to try to lay off that if
17 possible.

18 I think even right now the efficiency
19 issues we don't really know that or we haven't
20 quantitated that so I wouldn't go there either. Not
21 even soft pedal I wouldn't go there. I'm sure other
22 people have other things to include in that condition.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: Dr. Krupinski.

2 DR. KRUPINSKI: I think we should maybe
3 consider the possibility of adding the always never to
4 the software. Not only are you trained on it but,
5 say, maybe every 20th case because you can keep track
6 of who logs in, the reminder comes up so it's made a
7 part of their conscientiousness and you just don't
8 have it in that initial three-hour training session
9 because no one is going to read the manual. We know
10 that so if it's not in the initial three hours. In
11 addition as a later reminder.

12 DR. IBBOTT: Any other comments regarding
13 this condition? All right. Then I think we are ready
14 to vote on this one.

15 Dr. Krupinski.

16 DR. KRUPINSKI: Yes.

17 DR. CONANT: Yes.

18 DR. FERGUSON: Yes.

19 DR. SOLOMON: Yes.

20 DR. BLUMENSTEIN: Yes.

21 DR. TRIPURANENI: Yes.

22 DR. STARK: Yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: Unanimously in favor again.
2 Then we'll -- oh, I'm sorry. Dr. Mehta. He's
3 abstaining from all these, we think. One abstention.

4 Would someone like to entertain another
5 condition?

6 DR. FERGUSON: The issue of formalized
7 training for those that are going to use the device.
8 I like the idea of a CD-ROM. I don't have to spell
9 those out. Everybody knows what those would be. Most
10 of the panel feels that it's appropriate to spell out
11 a time. I don't think it's necessary for this device
12 personally.

13 DR. IBBOTT: Are you suggesting that the
14 condition mandate training when the device is sold?

15 DR. FERGUSON: Yes, I am.

16 DR. IBBOTT: Is there a second?

17 DR. KRUPINSKI: Second.

18 DR. IBBOTT: Dr. Krupinski. Anymore
19 discussion about this condition?

20 DR. TRIPURANENI: Could you elaborate, Dr.
21 Ferguson, what exactly in broad context. You want the
22 technicians to be trained and you want a CD-ROM to be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 given with some cases of false positives, false
2 negatives?

3 DR. FERGUSON: Yes. I think we've talked
4 about all of those things before. I can't remember
5 all of them or elaborate on them but I think they have
6 a clear idea of what we need to have rather than
7 somebody buys the instrument and puts it in. I think
8 we need a little more than just having a technician,
9 if you will, or an M.D. even. I don't know what level
10 this person is that goes in for two or three hours to
11 train. This will be protective for you as well as the
12 patients.

13 DR. IBBOTT: I'd like to comment. Also I
14 support this and I would like to see the sponsor
15 consider some sort of remote review. This is digital
16 data with DICOM. There probably are mechanisms that a
17 review could be done sort of looking over the shoulder
18 but from a distance so that it wouldn't necessarily --
19 the training session wouldn't be restricted to the
20 time that the company's representative is on site.

21 Any other comments? Okay. Then we'll
22 vote on this motion. Dr. Krupinski, we'll start with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 you again.

2 DR. KRUPINSKI: Yes.

3 DR. CONANT: Yes.

4 DR. FERGUSON: Yes.

5 DR. SOLOMON: Yes.

6 DR. BLUMENSTEIN: Yes.

7 DR. TRIPURANENI: Yes.

8 DR. STARK: Yes.

9 DR. IBBOTT: One abstention and the
10 remaining all vote yes. All right. Are there other
11 conditions?

12 DR. TRIPURANENI: I'd like to propose a
13 first marketing surveillance. The reason for that is
14 I think the amount of patients that they have even
15 though they are going to do the pre-marketing analysis
16 of the data, I'm afraid we may not have enough number
17 of patients to really tell us what is going on there.

18 They looked at the quadrants and the
19 number of nodules increase and all those things. When
20 you look at alive human beings and the clinical
21 impact, the significance is going to change. I think
22 it's going to be really small.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 I would like to propose that we give the
2 broad description to the FDA to kind of come up with
3 something in their best judgment post-marketing
4 surveillance where they can actually track that it
5 really have a clinical significance.

6 DR. KRUPINSKI: Second.

7 DR. IBBOTT: Thank you. Any discussion?

8 DR. CONANT: I think this is part of this.

9 I'm interested in the impact of the CAD and other
10 disease detection. I don't quite know how to do this
11 so I would want panel members to help with this. For
12 example, ground glass opacities and things like that.

13 I wonder if this might not impact one's detection of
14 some of these other things.

15 Again, it's broadening the population and
16 I would recommend that they do a study with less
17 strict criteria looking at a more prospective group
18 and analyzing the impact of the CAD on the
19 interpretation. Why you would have to look at the
20 interpretation before application of the CAD of all
21 diseases and look at it after. I don't know if that
22 is of interest to anyone else.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. SOLOMON: I think that is essentially
2 what the post-market study would be is to look at any
3 changes that come about as a result of the CAD usage.

4 DR. CONANT: Very general, right?

5 DR. KRUPINSKI: Not just on nodules but
6 other things as well.

7 DR. CONANT: Yeah, like mediastinal
8 adenopathy. It's that distraction aspect I think
9 someone brought up earlier.

10 DR. IBBOTT: It would be difficult for us
11 to design a useful study in the next 10 minutes.

12 DR. STARK: But is a potential condition
13 of approval to limit its approval to patients like
14 those studied and perhaps data can be shown to the FDA
15 so it could be approvable for use with contrast media.

16 We've heard that's possible and we haven't voiced any
17 objections to that but conditional approval that it
18 not be applied to patients with obvious artifacts,
19 other lung disease such as ground glass nodules or
20 pneumonia. It hasn't been studied in children and I
21 don't know if we're obligated to point that out and
22 ask for that.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. CONANT: They did have other diseases
2 in their first group but they didn't look at how the -
3 - there were others, emphysema, ground glass, post-op,
4 all that stuff. I'm not sure you can restrict it.

5 DR. STARK: Have they shown us enough that
6 they can market to all comers or is it a condition of
7 approval that this would be marketed to all?

8 DR. IBBOTT: This would be a new
9 condition.

10 DR. STARK: Either an amendment to the
11 existing motion or a new one.

12 DR. IBBOTT: The motion is for a post-
13 marketing study which would certainly address the
14 issues that you've mentioned.

15 DR. STARK: I didn't realize we had moved
16 to the --

17 DR. IBBOTT: Yes. This motion we are
18 discussing now is for a post-marketing study.
19 Surveillance.

20 DR. MOORE: Just to make a point of
21 clarification to Dr. Stark's comments, I think in the
22 company's labeling they have made it very clear that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 there are certain type of abnormalities that are not
2 appropriate for this device. I think some of the
3 labeling already takes into consideration some of the
4 points that you've raised.

5 DR. IBBOTT: Let's come back to the
6 discussion on the post-marketing surveillance. Then,
7 if necessary, we'll discuss the labeling again.
8 Further discussion? If not, let's vote on this motion
9 for post-marketing surveillance.

10 DR. KRUPINSKI: Yes.

11 DR. CONANT: Yes.

12 DR. FERGUSON: Yes.

13 DR. SOLOMON: Yes.

14 DR. BLUMENSTEIN: Yes.

15 DR. TRIPURANENI: Yes.

16 DR. STARK: Yes.

17 DR. IBBOTT: And one abstention. All
18 right.

19 DR. STARK: I'm sorry if I missed the
20 boat. I didn't realize we had closed the window and
21 moved on.

22 DR. IBBOTT: I don't think we've closed

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 any windows. We jumped to a motion to attach a
2 condition or recommendation for post-approval
3 surveillance but I don't think that prevents us from
4 considering more conditions to approval.

5 DR. STARK: Well, if I can, to catch up,
6 I've jotted down three to consider. All of these are,
7 of course, subject to the FDA staff's decision.

8 DR. DOYLE: Hopefully one at a time.

9 DR. STARK: Yes. I would suggest that
10 until it has been proved otherwise, which means in the
11 current condition it hasn't been proved, that there be
12 no claims, expressed or implied, of clinical
13 significance. And that there be no use of the term
14 significance.

15 I'm not just talking about lawyering this
16 but in spirit as well as the letter of this
17 recommendation, significance or the like except, as I
18 discussed before, in the very narrow reference to ROC
19 statistics and even then with some type of explicit
20 disclaimer that that's not -- was in a nonclinical
21 setting.

22 The only thing significant we've seen are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 statistics that are in a nonclinical setting and those
2 have help assure us of the safety and efficacy but I
3 don't think that should lead clinical radiologist to
4 have to juggle claims of significance.

5 DR. SOLOMON: Do you see that being
6 dependent upon the results of this clinical analysis
7 that we're talking about?

8 DR. STARK: I don't think so. I would not
9 say that satisfying anything that we have made as a
10 condition would release them from this condition, but
11 if the FDA finds additional data have established that
12 this is clinically significant, then I would say the
13 FDA should be free to waive that condition as a
14 separate condition.

15 DR. IBBOTT: All right. This is a
16 condition you would place on the labeling that the
17 manufacturer must meet for approval.

18 DR. STARK: Yes.

19 DR. IBBOTT: Are your other -- you
20 mentioned that you had three items. Do they also
21 address the labeling?

22 DR. STARK: They are labeling, yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: So perhaps we could group
2 them together?

3 DR. STARK: Well, they might fail one at a
4 time.

5 DR. IBBOTT: Then let's get a second on
6 this one.

7 DR. KRUPINSKI: Can I ask is labeling the
8 same as advertising?

9 DR. DOYLE: It comes under labeling

10 DR. KRUPINSKI: It is? Okay.

11 DR. IBBOTT: Is there a second?

12 DR. FERGUSON: Second.

13 DR. IBBOTT: All right, Dr. Ferguson.
14 Okay. Any further discussion about this? This would
15 be another condition placed on approval to presumably
16 modify the labeling -- existing labeling and certainly
17 when designing any new labeling to avoid claims of
18 clinical significance.

19 DR. CONANT: I'm not quite sure we can do
20 that yet. I want to see their data first. I think
21 that could come later but I don't want to close the
22 door on their data so I would be hesitant to vote yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 I'm sorry.

2 DR. STARK: I'm just saying if there is no
3 more data or if the FDA finds that data insufficient.

4 DR. CONANT: Yes, sure. I trust that the
5 FDA will do that but I'm not sure -- yeah, it's kind
6 of a condition on a condition. It's sort of one step
7 at a time. I think we have asked a big condition of
8 looking at the data and that may all not show any kind
9 of significance, clinical or other that we are asking
10 for and then that becomes obvious. I don't get that
11 really.

12 DR. IBBOTT: Dr. Blumenstein.

13 DR. BLUMENSTEIN: I'm going to vote no on
14 this because I feel that I trust the FDA to deal with
15 that given that we have a preapproval condition for
16 clinical data.

17 DR. IBBOTT: Any further discussion?

18 DR. CONANT: One other. Sorry. David, in
19 spirit I agree very much with what you're saying but
20 we already voted and yes'ed a condition on labeling
21 saying they had to take the stuff out. We did that a
22 couple steps ago. I think we have suggested that we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 really feel this is important by voting on that. And
2 then, again, the FDA is going to take it from there.

3 DR. IBBOTT: I think I feel the same way
4 that we have asked them to do some more analyses of
5 the existing data. The FDA may determine that
6 detracts from the significance.

7 DR. STARK: I'd be happy to withdraw the
8 motion if there is a consensus, or we better take a
9 vote.

10 DR. IBBOTT: I think we can just go ahead
11 and vote if that's all right. I should ask, though,
12 is there anymore discussion before we vote? Dr.
13 Krupinski?

14 DR. KRUPINSKI: No.

15 DR. CONANT: No.

16 DR. FERGUSON: Yes.

17 DR. SOLOMON: No.

18 DR. BLUMENSTEIN: No.

19 DR. TRIPURANENI: No.

20 DR. STARK: Yes.

21 DR. IBBOTT: There were two yeses and five
22 nos and one abstention. So that motion is defeated.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Are there motions for other conditions to attach to
2 the approval.

3 DR. STARK: I have two more and I'll be
4 brief.

5 DR. IBBOTT: Sorry.

6 DR. STARK: That's okay. I would ask that
7 it be added to the label something to the effect or
8 spirit of the following words. "Careful rereading or
9 second reading may be equally or more safe and
10 effective in a clinical setting."

11 DR. DOYLE: Could you say that again?

12 DR. STARK: "Careful rereading or second
13 rereading may be equally or more safe and effective
14 than a computed second reading in a clinical setting."

15 DR. IBBOTT: Is there a second for this
16 motion?

17 DR. FERGUSON: Is that a directive to the
18 radiologists rather than the instrument?

19 DR. STARK: It's a directive for -- I'm
20 intending it, and forgive me for exploring this, but
21 what a radiologist faced with purchasing this or using
22 it will be told. I am proposing that he should be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 told that if he simply reread the scan himself or had
2 a colleague double read it, that actually might be
3 more efficient and safe than this product.

4 DR. KRUPINSKI: But you don't have any
5 data to support your contention.

6 DR. STARK: That's why I said may be.
7 They don't have any data to support theirs. I'm
8 trying. I've only got one more.

9 DR. TRIPURANENI: I have difficulty with
10 this.

11 DR. IBBOTT: We're looking for a second.

12 DR. STARK: If I don't have a second it
13 goes. We'll move on.

14 DR. IBBOTT: No seconds. All right.

15 DR. STARK: Last, it's the same family.
16 I'm just probing this boundary between nonapprovable
17 and approvable with conditions. Not demonstrated safe
18 or effective until there's data in patients with
19 artifacts, concomitant lung disease, contrast media
20 use, or pediatric populations.

21 DR. KRUPINSKI: Doesn't this come under
22 the post-surveillance type stuff that we were asking

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 for?

2 DR. STARK: I thought labeling. Condition
3 of the labeling.

4 DR. CONANT: I think we are asking again
5 for the data to be analyzed and included in that by
6 case is looking at -- I mean, there were cases with
7 artifacts and things like that. I think that is part
8 of what the false negative and false positive analysis
9 is going to provide us with. Again, it's a limited
10 case set but depending on what that shows, the next
11 set may be --

12 DR. STARK: If it is understandable to the
13 FDA that we are assuming they are going to check this,
14 I'm saying that we haven't seen these data and I was
15 asking as a condition that the FDA ask to see it. I
16 was just making that a motion. I mean, I know we can
17 assume that they'll do this anyway.

18 I'm just trying to make it a specific
19 direction. Of course, this is all advice and they can
20 ignore all of this but if there is a consensus that
21 they should do this, then that is, I think, the
22 purpose of the motion I'm making which is to ask them

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 to.

2 DR. IBBOTT: Go ahead.

3 DR. CONANT: Could it be that we could put
4 this in the first condition which was the first
5 preapproval condition that was to go back and look at
6 these cases and we talked about by-case compared to
7 by-nodule and quadrant, etc. Do you want to step back
8 and beef that one up a little bit?

9 DR. SOLOMON: I think procedurally that
10 will be a problem.

11 DR. CONANT: We can't do that? Okay.

12 DR. IBBOTT: We can address this motion
13 with the understanding that, in fact, that is what
14 will happen. We can deal with this motion
15 independently at the first.

16 DR. CONANT: Could you reword your motion
17 or could you restate it again? I didn't mean reword
18 it. Just say it again.

19 DR. STARK: Yeah, and certainly someone --
20 I think all of these we are understanding that we
21 haven't wordsmithed these. I'm simply suggesting that
22 until the FDA sees data, which we hope is available,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 it should be a condition of premarket approval that
2 the product will be labeled as not demonstrated safe
3 or effective, or safe and effective with the use of
4 contrast media in the presence of artifacts or
5 concomitant lung disease or in pediatric patients.

6 DR. KRUPINSKI: From a nonclinician --

7 DR. FERGUSON: It's totally unexplored. I
8 don't think we can suggest that the FDA look at these
9 because I don't think we can put that into a formal
10 motion because those things are unexplored as far as I
11 know.

12 DR. CONANT: I think that you're saying
13 that the labeling should read this but the point is if
14 it doesn't get approved and it doesn't follow this
15 condition that we first said about reanalyzing the
16 data, there's no labeling here because it's not going
17 anywhere. You're already jumping to labeling based on
18 the data. It's kind of contradictory

19 DR. STARK: I am suggesting that if it is
20 approved based on whatever, but we see no data on
21 contrast media, artifacts, pediatrics, or lung disease
22 that the labeling contain these restrictions.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. CONANT: If we see no data on those
2 things.

3 DR. STARK: If the FDA is not satisfied
4 with the data which includes not seeing any further
5 data.

6 DR. CONANT: Okay.

7 DR. IBBOTT: The sponsor has indicated
8 that their data do include cases with contrast and
9 cases with artifacts. Are you suggesting that when
10 they do the reanalysis that we've already asked them
11 to do that they also pay attention or conduct an
12 analysis to look specifically at the impact of
13 artifacts or with versus without contrast?

14 DR. STARK: Yes. I'm saying that they say
15 they have data that we haven't seen and that if they
16 -- offering them a choice of either satisfy the FDA
17 that when they offer statistics on their data that
18 it's convincing and labeling shouldn't apply or simply
19 say we can market it and simply market it with the
20 warning that if you patient has artifacts we haven't
21 demonstrated safety and efficiency -- sorry, safety
22 and efficacy.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: So, yes. I'm not going to
2 try and rephrase your motion but I believe that you're
3 asking that the reanalysis we've asked them to do
4 contain those elements to look at artifacts,
5 contrasts. There were no pediatric patients so we
6 won't include that.

7 Then depending on the results the labeling
8 should be modified to indicate that the device is not
9 appropriate for pediatric patients. For example, if
10 the data don't support its use in pediatric patients.
11 Is that right?

12 DR. STARK: That's correct.

13 DR. DOYLE: We need a second

14 DR. IBBOTT: Yes. We need a second.

15 DR. KRUPINSKI: The pediatric issue, I
16 just talked to a clinician, could be significant. I
17 mean, if the CAD --

18 DR. CONANT: I'm not really sure about
19 this. I haven't looked at a pediatric chest -- well,
20 actually I do on the weekends.

21 DR. IBBOTT: No one will ever know.

22 DR. CONANT: It won't get out of this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 room. Obviously kids were not analyzed. It was 19
2 and above so obviously pediatrics should be a
3 contraindication. That should be included in the
4 labeling. I think we all agree about that definitely.

5 DR. STARK: I think if we don't make a
6 motion it's not obvious at all because I could wear
7 the other hat.

8 DR. CONANT: I think I brought that up
9 earlier when I said that has to be one of the things
10 that we address with looking back over the data. At
11 least, I'm sorry if I didn't. I don't remember what
12 the transcript was but that's got to be something in
13 the label and it's not in the contraindication line.
14 The artifacts we could talk about as a motion. That
15 sounds like a good idea. Maybe separate out from the
16 artifacts and other things.

17 DR. STARK: I don't know where we are in
18 pediatrics. Do we need a separate motion? Are you
19 suggesting that I bifurcate this already complicated
20 thing? I'm just trying to point the FDA to satisfy
21 yourself on these things or exclude them.

22 DR. CONANT: I think there's a difference

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 here of what there may be data on versus what there
2 isn't a chance in hell they are going to be able to
3 analyze because there's no babies or kids. I think it
4 is different. I think it's two separate issues so I
5 would say separate it.

6 DR. STARK: If you don't mind, why don't
7 you make the motion on the pediatrics.

8 DR. CONANT: Contraindication no. Is it
9 19 and over? Eighteen. Sorry. No one under 18
10 should be analyzed with this.

11 DR. STARK: I'll amend my motion by
12 dropping the word pediatrics. We can deal with that
13 then and then you can have --

14 DR. IBBOTT: You've withdrawn. It wasn't
15 seconded so that motion is withdrawn.

16 DR. STARK: I think we are still
17 discussing it. I would like to say that until the FDA
18 is satisfied from the existing data set or some other
19 data set but not -- I'm suggesting it's a restriction
20 because we haven't seen the data here that it be a
21 condition that it be marked not demonstrated safe or
22 effective in patients with concomitant lung disease or

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 with lung disease -- known lung disease, scanning
2 artifacts, or with contrast media. Again, we know
3 they have data on contrast media. I hope it will
4 convince the FDA but I'm asking that we require that.

5 DR. CONANT: Should we put pediatric under
6 18 first?

7 DR. STARK: I eliminated that from my
8 motion hoping that you would carry forward with yours
9 afterwards.

10 DR. CONANT: Okay.

11 DR. IBBOTT: You're seconding his motion?

12 DR. CONANT: No. He told me to do it
13 independently so I just did that.

14 DR. IBBOTT: We need a second for the
15 motion he just made.

16 DR. STARK: I think I'm trying to bargain
17 with you.

18 DR. IBBOTT: You guys have to decide.

19 DR. CONANT: I think that is still part of
20 the one we already passed where we've asked for
21 further analysis of the existing data. I think we
22 have already covered that. That's why I'm not

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 seconding it because I think we are already asking
2 them. I mean, if you reanalyze the data and they find
3 that they can't support what you want, then yours is a
4 condition on the condition that they don't find it.
5 But if they do the analysis and find it, then your
6 condition isn't needed.

7 DR. STARK: I think it's sufficiently
8 likely that they are not going to have statistically
9 convincing data on artifacts or post-op patients or
10 patients with pneumonia. I am trying to attach a
11 condition that will help the FDA simply say put in the
12 label you should be careful and not use it in these
13 patients because it's unproved. I believe they have
14 data on contrast media but I'm lumping them all of
15 them in the same.

16 I'm saying these are identifiable
17 important subsets just like the pediatrics issue. I'm
18 simply saying specifically look at the analysis for
19 these things and assuming that there is not
20 satisfaction here in some of them, please label the
21 product appropriately.

22 DR. IBBOTT: Dr. Tripuraneni.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. TRIPURANENI: I think there are
2 lumpers and splitters. I'm a lumper. I think FDA is
3 hearing what we are saying and I think rather than go
4 down to the final nitpicking and actually spell out
5 everything, I would rather leave it to the broad
6 discretion of the FDA to decide the best in their best
7 judgment. I really don't support this element.

8 DR. IBBOTT: We don't have a second yet.
9 Is anyone willing to second the motion? All right.
10 Does someone want to make the other motion regarding
11 pediatric patients?

12 MS. BROGDON: May I make a comment first?
13 I just wanted to describe how we treat
14 contraindications. We use the term contraindication
15 to mean something you shouldn't do because there are
16 data that say you must not do that. There must have
17 been some sort of demonstration of harm. Short of
18 that, there are warnings and there are cautions and
19 other things that you can say in the labeling that
20 don't reach the level of contraindication.

21 DR. IBBOTT: Good distinction. Thank you.

22 DR. CONANT: Maybe this is a post-

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 marketing study. They've got to apply it to kids. I
2 don't know if that -- maybe it's just a warning saying
3 there is no data to support this use under 18.

4 DR. KRUPINSKI: Somewhere it has to be
5 stated or brought out in the manual or in the warnings
6 or somewhere there is obviously not a contraindication
7 but it should be there somewhere.

8 DR. STARK: The rocket scientist in me
9 says that why are children different than adults and
10 it's probably going to work. But as a human, as a
11 parent, I have a hard time saying these are just small
12 adults. On the other hand, the admonitions of lumping
13 and leaving it to the FDA, this is all on record, I've
14 spoken. My conscious is satisfied. I'm going to
15 leave it to someone else to make a motion.

16 DR. IBBOTT: This is certainly something
17 that could be included in a recommendation for a post-
18 market study and I think we have probably done that or
19 implied that.

20 Any other conditions people would like to
21 attach?

22 DR. CONANT: Have we figured out the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 pediatric one?

2 DR. IBBOTT: We have not. I have made the
3 assumption that the sponsor and the FDA understand
4 from the discussion that a post-market study would
5 include pediatric patients.

6 Yes, Nancy.

7 MS. BROGDON: I'm advised that since the
8 sponsor has not indicated that it is -- could be used
9 in pediatric patients, FDA would in most circumstances
10 include some sort of statement in the labeling that it
11 has not been studied and it is not intended for use in
12 children.

13 DR. CONANT: There you go. I'll second
14 that motion.

15 DR. STARK: I say yes.

16 DR. IBBOTT: The relief is palpable. I
17 think unless there are other motions for conditions,
18 we are ready to vote on the main motion which is for
19 approval with conditions, the conditions being those
20 we've just discussed.

21 DR. DOYLE: The ones that were seconded
22 and approved.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. IBBOTT: That's right. So we do have
2 the motion and so unless there is any further
3 discussion on the main motion, we'll proceed to a vote
4 on the motion to approve with -- as approvable with
5 conditions.

6 DR. KRUPINSKI: Yes.

7 DR. CONANT: Yes.

8 DR. FERGUSON: Yes.

9 DR. SOLOMON: Yes.

10 DR. BLUMENSTEIN: Yes.

11 DR. TRIPURANENI: Yes.

12 DR. STARK: Yes.

13 DR. IBBOTT: And with Dr. Mehta's
14 abstention the rest of the votes are all in favor so
15 that motion carries. We have declared this approvable
16 with conditions and we've approved a number of
17 conditions. At this point we go around the room and
18 ask the voting members to explain the reasons for
19 their vote. Dr. Krupinski, again, we'll start with
20 you and ask you to identify the reason for your vote
21 on the decision as approvable with conditions and also
22 on the recommendations. You can probably summarize

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 your reasoning.

2 DR. KRUPINSKI: Why doesn't somebody else
3 start because, I mean, it seems like I would just say
4 the entire conversation we just had all over again. I
5 agreed with all the changes or the conditions that we
6 brought up. I think they satisfied the questions we
7 had throughout the day and so I voted yes.

8 DR. IBBOTT: I think that's fine.

9 Dr. Conant.

10 DR. CONANT: That's basically the same
11 with me. I'm just concerned about how the statistics
12 -- how the analysis will differ with case-based versus
13 actionable nodules and quadrants. I, again, applaud
14 you all for the beautiful study you have done and
15 answering the questions given to you by the FDA.

16 I hope you have this data to show us
17 because I think this could be a wonderful tool. As
18 these things go they only get better over time. I
19 think it really could have benefit to patients. But I
20 really need that data.

21 DR. IBBOTT: Dr. Ferguson.

22 DR. FERGUSON: I agree with everything she

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 said.

2 DR. IBBOTT: Dr. Solomon.

3 DR. SOLOMON: I think you should be
4 applauded for dealing with the problem that is an
5 important clinical problem. I think there are two
6 issues that the panel is charged with. The first one
7 being safety. I think the issues of always and never
8 are the issues on safety and I thin there are ways you
9 can address these and we have discussed those today.

10 The second issue that we are charged with
11 is efficacy. I think the key word there is clinical
12 efficacy and I'm not sure we were able to see exactly
13 the clinical efficacy with the way the data was cut up
14 and divided so that we think that if you were to look
15 at it again with that in mind, it might be able to get
16 through to the FDA.

17 DR. IBBOTT: Dr. Blumenstein.

18 DR. BLUMENSTEIN: I was disappointed that
19 neither the sponsor came forward with clinical
20 analysis, and I'm also disappointed that the FDA
21 didn't require that of them, especially since our
22 criteria before approval for efficacy has clinical

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 efficacy mentioned in it. I'm also discomforted by
2 the unique properties of this study designed that may
3 lead to inaccurate assessment of the ROC methodology.

4 DR. IBBOTT: Dr. Tripuraneni.

5 DR. TRIPURANENI: I would like to
6 congratulate R2 for actually coming up with this new
7 concept. You are a pioneer in the CAD and it's good
8 and bad. It's bad that being the first one we are
9 going to hold you to a higher standard because we have
10 ideas about what is right and what is wrong. Somebody
11 else that is going to come after you their life would
12 be a lot easier because they are going to learn from
13 your mistakes. On the other hand, I think you have
14 done a very good job on this.

15 I personally think actually any
16 improvement in the process actually will ultimately
17 lead to the improvement in care. I think it's
18 important actually that we continue to pursue to
19 improve the processes that ultimately improve the
20 care. That is the reason why I think we attach those
21 amendments and I firmly believe it will make a
22 positive impact on the patients. That is the reason

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 why I vote yes with amendments.

2 DR. IBBOTT: Dr. Stark.

3 DR. TRIPURANENI: Can I just add one
4 thing? I really would like to see FDA asking for
5 clinically efficacy because I participated in the
6 Cardiovascular Devices Panel, as I say, participated
7 on the other side of the table a couple of times and
8 they kept pointing the table to where is the clinical
9 data, where is the clinical efficacy. I would ask the
10 sponsors to give us some clinical data when
11 appropriate.

12 DR. IBBOTT: Dr. Stark.

13 DR. STARK: Well, first, as lead clinical
14 reviewer I would like to thank everybody on the panel,
15 everybody in the audience, especially R2 for listening
16 carefully and responding to my many adversarial
17 comments. I think that was part of my role here today
18 to be both the adversary as well as one of the voting
19 judges. I thank the chair. It's been a very
20 efficient, respectful proceeding.

21 Having said that, I, again, agree with Dr.
22 Blumenstein's assessment as a statistician. I note

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 that both the lead reviewers had a viewpoint strongly
2 held that was overwritten by the rest of the committee
3 and I can now step back and agree with Dr. Conant who
4 has emphasized, and those reading the transcript would
5 not have seen her facial expression and the movement
6 of her fist in terms of emphasizing that we are now
7 relying on the FDA staff to continue diligently what
8 they have already said is a nearly overwhelming task.

9 Not just for their manpower and resources but for
10 their range of skills. I think this committee and the
11 people in this room and a larger group, I believe,
12 needed to address this again to relook at these data
13 but I accept that I have been outvoted and we will now
14 rely on what is clearly a very competent, energized
15 and well-supported FDA staff to essentially accomplish
16 the same thing that Dr. Blumenstein and I were pushing
17 for but as Dr. Conant and the majority have voted.
18 Thank you.

19 DR. IBBOTT: Thank you. I would like now
20 to ask the nonvoting representatives to comment on the
21 recommendations that have been made. Ms. Moore.

22 DR. MOORE: Although I did not vote, I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 think I would have been in agreement with the panel on
2 recommending this for approval. I think that any
3 improvement in our ability to detect nodules that are
4 not being detected is an important step forward and I
5 commend R2 on their efforts and view of the data and
6 trying to move this technology forward.

7 DR. IBBOTT: Mr. Burns.

8 MR. BURNS: The conditions satisfy the
9 concerns that I had regarding the study size and the
10 data set and the small change in the area under the
11 ROC. I think by analyzing the data we will see if
12 there is some better significance with the data.

13 DR. IBBOTT: Good. Thank you. I would
14 like to just give Dr. Mehta a chance to make any
15 comments he might have.

16 Dr. Mehta, do you have any comments?

17 DR. MEHTA: No. I think I just want to
18 thank Geoff Ibbott for doing an excellent job of
19 running the meeting. Although I didn't hear all the
20 proceedings, I think I heard enough to concur with
21 what actually happened. Thank you, everybody.

22 DR. IBBOTT: Thank you, Dr. Mehta.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Mr. Doyle.

2 DR. DOYLE: Before we adjourn for the day,
3 I would like to remind the panel members that they are
4 required to return all the materials that were sent
5 pertaining to the PMA itself. Materials you have with
6 you may be left at your table and any other should be
7 sent back to me at the FDA as soon as possible.

8 DR. IBBOTT: Thank you. Finally, I would
9 like to thank the speakers and the members of the
10 panel for their preparation and participation in this
11 meeting. I would like to especially thank Dr. Stark
12 and Blumenstein for serving as lead reviewers for the
13 panel and doing an excellent job of summarizing this
14 and helping the rest of us understand it.

15 And I would like to thank the sponsors for
16 graciously responding to the many questions that were
17 aimed at them and for putting on an excellent
18 presentation.

19 Since there is no further business, I
20 would like to adjourn this meeting of the Radiological
21 Devices Panel. Thank you.

22 (Whereupon, at 5:20 p.m. the meeting was

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1

adjourned.)

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com