

1 the appropriate analysis because it is not relevant to  
2 the patient population who has the disease. I wish I  
3 could make suggestions as to how the data should be  
4 analyzed but it would be, I think, appropriate to say  
5 that we need a lot more data that would allow an  
6 analysis before reaching a conclusion.

7 DR. KROLL: Do we have additional  
8 comments?

9 DR. EVERETT: Just one. This is James  
10 Everett. I want to say that I agree because if our  
11 statisticians say the data is only suitable for males  
12 and then one of the panelists says this is just young  
13 males and this is the group that doesn't even have the  
14 disease for the most part. Again, I just want to say  
15 I think he's absolutely correct.

16 DR. KROLL: Any other comment? I'm in  
17 agreement, too, with Dr. Packer. Does that  
18 sufficiently answer the question, Dr. Gutman?

19 DR. GUTMAN: Yes, that's fine.

20 DR. KROLL: Okay. Let's go to question 5.  
21 This is too long to read. There is considerable  
22 overlap between the NYHA CHF classes, and FDA is  
23 concerned that gender differences, assay precision,  
24 and drug recovery can contribute to additional overlap  
25 or misclassification. Should the BNP results

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1 stratified by the NYHA classification remain in the  
2 labeling as is, be modified in some ways you could  
3 suggest, or be deleted? Yes, Dr. Clement.

4 DR. CLEMENT: I recommend leaving it.  
5 This is one of the positive aspects of this study is  
6 that there is a strong association with classes.  
7 That's something that's very well ingrained in the  
8 literature in terms of how we stratify patients on  
9 severity, so I think that's a plus in terms of  
10 performance even though it may not be perfect.

11 DR. KROLL: Yes, Dr. Brinker.

12 DR. BRINKER: Brinker. I think I agree  
13 but for different reasons. I think that leaving the  
14 association will reinforce the idea of potential users  
15 that the test may, in fact, only be reliable, or be  
16 most reliable in people with manifest heart failure in  
17 this degree of symptomatology referencing basically  
18 the LVEDP at that particular time.

19 If they get treated, the Class III gets  
20 treated to a Class I. He may not, or she, Black or  
21 White, Asian or Eskimo, may not have a positive BNP.  
22 I think this will sort of reinforce that this should  
23 be at this stage of our knowledge base. Their own  
24 data, I think, would back this up to be used for  
25 relatively severely symptomatic patients and this

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1 basically shows the biggest cutoff.

2 DR. KROLL: Anybody else on the panel have  
3 any additional comments?

4 DR. ROSENBLOOM: Rosenbloom. I'll be  
5 interested in seeing the preliminary response I had,  
6 which was there was no difference in those with  
7 diabetes. It would be interesting to note if the --  
8 perhaps the cardiologists all know this, that the NYHA  
9 classification applies to those with diabetes as well.  
10 Does it?

11 DR. BRINKER: The Canadian classification  
12 which refers to angina doesn't. I think heart failure  
13 is less discriminatory and I guess Milton would be the  
14 best person to answer that question.

15 DR. PACKER: The associate disorder  
16 shouldn't make a difference. It's just the assessment  
17 of symptoms. There is no information that we have  
18 that diabetes either enhances or diminishes the  
19 expression of those symptoms.

20 DR. KROLL: I'd actually like to make a  
21 comment, because I really agree with the first  
22 sentence which is the fact of gender differences.  
23 There's a big problem here, I think, with assay  
24 precision or imprecision and potentially drug  
25 interferences or other affects that are occurring that

1 can smear the differences between these groups if we  
2 measure with BNP.

3 I think that needs to be stressed that  
4 even though they're coming up and showing that, maybe  
5 perhaps you can stratify which class someone falls  
6 into by using the proposed method, that it has to be  
7 taken into consideration that there is significant  
8 error on an individual measurement and that is  
9 contributed by potential bias of the actual assay, the  
10 imprecision, and some of these other factors that have  
11 been mentioned.

12 Anybody else have any other comments?  
13 Have we sufficiently answered this question for you?  
14 Okay. Fine.

15 Now we need to go ahead and proceed with  
16 the final recommendations and vote. I'll turn things  
17 over to Veronica who can read how we are going to do  
18 this next step.

19 MS. CALVIN: Panel members, you have this  
20 information before you as well as a flow chart that  
21 will be following. The medical device amendments to  
22 the Federal Food, Drug, and Cosmetic Act as amended by  
23 the Safe Medical Devices Act of 1990 allows the Food  
24 and Drug Administration to obtain a recommendation  
25 from an expert advisory panel on designated medical

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1 device premarket approval applications that are filed  
2 with the agency.

3 The PMA must stand on its own merits and  
4 your recommendation must be supported by safety and  
5 effectiveness data in the application or by applicable  
6 publicly available information.

7 Safety is defined in the Act as reasonable  
8 assurance based on valid scientific evidence that the  
9 probable benefits to health under conditions on  
10 intended use outweigh any probable risks.  
11 Effectiveness is defined as reasonable assurance that  
12 in a significant portion of the population the use of  
13 the device for its intended uses and conditions of use  
14 when labeled will provide clinically significant  
15 results. Your recommendation options for the vote are  
16 as follows.

17 (1) Approval if there are no conditions  
18 attached.

19 (2) Approvable with conditions. The panel  
20 may recommend that the PMA be found approvable subject  
21 to specified conditions such as physician or patient  
22 education, labeling changes or further analysis of  
23 existing data. All of the conditions should be  
24 discussed and voted on one by one by the panel.

25 (3) Not approvable. The panel may

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1 recommend that the PMA is not approvable if the data  
2 do not provide reasonable assurance that the device is  
3 safe or if a reasonable assurance has not been given  
4 that the device is effective under the conditions of  
5 use prescribed, recommended, or suggested in the  
6 proposed labeling.

7 Following the voting, the chair will ask  
8 each panel member to present a brief statement  
9 outlining the reasons for their vote.

10 DR. KROLL: What I'd like to do now is to  
11 call for a motion from the voting panel members as to  
12 one of these three areas; approval, approval with  
13 conditions, or not approval.

14 Yes, Dr. Packer.

15 DR. PACKER: I'll make a motion for not  
16 approvable.

17 DR. KROLL: All right. Do we have a  
18 second for that motion?

19 DR. CLEMENT: Second.

20 DR. KROLL: We have a second from Dr.  
21 Clement. Now I open it up to the panel to discuss  
22 this. Would any of the panel members wish to discuss  
23 this motion. Yes, Dr. Brinker.

24 DR. BRINKER: Well, I'd like to oppose the  
25 motion and I'd like to give my reasons why. I think

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1 that there is some value to this test. It is not to  
2 detect the presence of heart failure. It's not to  
3 detect Class I or Class II heart failure.

4 I think the whole idea of classification  
5 is wrong but it may be helpful in certain patients in  
6 a differential diagnosis of symptoms that are  
7 compatible with heart failure in an acute situation.  
8 My own feeling is that it might be helpful, although  
9 this hasn't been demonstrated, in the follow-up of  
10 patients with heart failure. I think there is little  
11 downside.

12 I would have voted for approval, or I  
13 would have made the motion for approval, with  
14 conditions and those conditions should be a very  
15 cautiously worded labeling which doesn't say that this  
16 device makes the diagnosis of heart failure, nor would  
17 it say anything else specific other than it may be  
18 helpful in certain patients in the diagnosis and  
19 management of severe heart failure.

20 I would also hasten to ask the sponsor to  
21 do the appropriate studies to improve their labeling  
22 but with a very limited labeling. My feeling is that  
23 the device will be available to people who want to  
24 make use of it but would not, I don't think, over use  
25 it until the appropriate studies were done.

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1           Quite frankly I'm impressed by the fact  
2 that this kind of assay is used worldwide in the  
3 literature supporting the PMA. Even though it wasn't  
4 a specific assay it was very interesting and favorably  
5 impressed me. I think there is little downside to  
6 having this available. I don't think anybody is going  
7 to be harmed by this. That would be my point of view.

8           I recognize fully that the study done to  
9 bring this to this PMA discussion was not well  
10 focused, not well thought out, and is actually  
11 inadequate to make the scientifically rigorous  
12 demonstration that we would all want but I think it's  
13 acceptable under the broad umbrella of what we're  
14 working with.

15           DR. HENDERSON: I would agree. I actually  
16 would have voted for approval with conditions because  
17 I think it is -- I was impressed with the literature  
18 that we were sent that it could well be a useful tool  
19 in screening patients who present with a diagnostic  
20 dilemma in trying to sort out all the details sort of  
21 immediately.

22           While I think the data certainly needs to  
23 be increased, the number of patients who are at risk  
24 with the disease needs to be further evaluated and to  
25 make it far more applicable to a general population.

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1 I think in general the information is, I think,  
2 exciting.

3 DR. ROSENBLOOM: Rosenbloom. As I read  
4 the conditions of approvable with conditions, it says,  
5 "Specified conditions such as physician or patient  
6 education, labeling changes, or a further analysis of  
7 existing data." It does not say that we can give the  
8 condition of further post-marketing data collection.  
9 Could I get a clarification of that?

10 DR. GUTMAN: Is that right, Veronica?

11 MS. CALVIN: That is an option.

12 DR. ROSENBLOOM: That is an option? Then  
13 under those circumstances for the reasons cited by Dr.  
14 Brinker, I would also favor approval with conditions  
15 as long as we can do that.

16 DR. KROLL: Additional discussion.

17 DR. CLEMENT: Actually, if we change the  
18 definition of approval with conditions, I think I may  
19 even withdraw my second if we can say that they can be  
20 approved if they collect more data particularly in  
21 different population groups.

22 DR. KROLL: Let's call the question.

23 DR. PACKER: Can I ask one clarification  
24 from the agency? It's not clear to me why sponsors  
25 are asked to do studies to support a package if

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1 advisory committees are allowed to approve them  
2 pending collection of the appropriate data.

3 In other words, sponsors either have  
4 collected the appropriate data in the appropriate  
5 manner or they haven't. What I hear this committee  
6 saying is we intuitively think this is a good idea but  
7 they haven't collected the data so we'll approve it so  
8 they can now actually do the right studies. That  
9 seems weird to me. It seems backwards.

10 It seems as if there shouldn't be an  
11 application to do studies. There should first be an  
12 application for approval and then you can be on the  
13 market and then do the right studies. How can that  
14 make sense?

15 How can we as a committee say that what  
16 this process is all about is that we think it's just  
17 a generally good idea and we think of all the things  
18 that this test could possibly be used for although  
19 there are no data to support that. We just  
20 intuitively think it's a good idea.

21 The sponsor intuitively thought it was a  
22 good idea before they started the studies. We're  
23 going to say you're approved. You should go ahead and  
24 market this but we want you then to do the studies you  
25 should have done as part of this application. That

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1 doesn't make sense.

2 DR. GUTMAN: Well, actually that's not the  
3 spirit of the deal. If you're going to approve it,  
4 there has to be a core when you approve it. What  
5 you're saying is there are missing elements, not a  
6 missing core and that core can be gaped by additional  
7 studies. In some cases those might be demographic  
8 studies or real world studies.

9 If you think that gap is really serious,  
10 then that gap should be bridged before we actually  
11 approve the product. I think that's what Veronica is  
12 saying. If you think that gap doesn't preclude you  
13 from going ahead and using it, then you could ask for  
14 the studies to be done after the approval.

15 If you think the core of this just doesn't  
16 support the claim and doesn't meet the safety and  
17 effectiveness, then you ought to vote it down. It's  
18 a question of if there's no core here, then we're not  
19 looking for a gap.

20 If there's a core here that you are  
21 comfortable with and there's a gap, you supplement  
22 with additional studies of a particular age or  
23 particular gender or particular race. It is a grey  
24 zone sort of like beauty. It's a hard call.

25 DR. KROLL: Yes, Dr. Everett.

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1 DR. EVERETT: I tend to agree again. I  
2 guess that may be obvious because here the problem is  
3 the safety and effectiveness has not been proven so  
4 what am I going to approve? First of all, there is  
5 the safety, in the best case scenario, only in  
6 young men where the disease is not prevalent.

7 No data. I'm not imagining this now.  
8 They put the data up here. There is no data to  
9 support that at all. When I think of approve with  
10 conditions, at the very least safety and effectiveness  
11 has been proven in a large number of people. That's  
12 not the case here. At least the people where the  
13 disease is prevalent.

14 First of all, the disease is not prevalent  
15 in young men. It's easy to show the difference  
16 between two extremes, dead or alive, CHF or no CHF.  
17 The grey zone really is in diagnosing people who come  
18 in and it's not clear what they have. I'm going to  
19 use a test that says, at best, this test works if it's  
20 clear they have it and it's clear they don't. I don't  
21 need the test in those conditions.

22 I do family practice and treat patients of  
23 all ages. I work in the emergency room. I'm in  
24 charge of the emergency room and we don't use test  
25 like that because that will land us in court.

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1                   If I'm going to think of the best interest  
2 of the people in this country, I can't walk out of  
3 here and say I approve the test that was only proven  
4 to be safe and effective in young men you don't have  
5 the disease. There's no rational basis for that. I  
6 think the literature does but the company doesn't so  
7 the database that they gave us doesn't show that.

8                   DR. KROLL: I think Dr. Comp wants to make  
9 a comment and then I think we need to go take a vote.

10                  DR. COMP: I'd echo those statements. We  
11 don't know if it has any utility in mild congestive  
12 heart failure which is the vast majority of people.  
13 We have serious concerns will it provide any real  
14 diagnostic value in old men and old women and that's  
15 the problem.

16                  Right then we are stripped down to  
17 approving a test that measures the level of a peptide  
18 in blood and I don't think that would be particularly  
19 satisfactory either. At this point that's apparently  
20 what it does and I think it probably does it pretty  
21 well.

22                  DR. KROLL: Okay. I think it's time to go  
23 ahead and take a vote.

24                  PARTICIPANT: We have a motion.

25                  DR. KROLL: All in favor of the motion of

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1 not approval please raise your hand.

2 PARTICIPANT: It hasn't been seconded.

3 DR. KROLL: Yes, it has.

4 MS. CALVIN: Let me clarify. You can't  
5 take back your second right now. The discussion was  
6 on the motion that's been seconded. We're going to  
7 vote. If it's defeated, we'll entertain a new motion.

8 DR. KROLL: All right. By show of hands  
9 all in favor of the motion not to approve please raise  
10 your hand. I have six. All opposed to the motion.  
11 That's three. The motion passes.

12 I think now we would like to hear some  
13 brief comments from the sponsor if he has anything to  
14 say.

15 DR. BRUNI: I believe in regard to some of  
16 the shortcomings that have been identified in the  
17 clinical study, this product still has utility as an  
18 aid in the diagnosis of congestive heart failure.

19 This is well substantiated in the  
20 literature and with the data that we've provided in  
21 looking at apparently healthy people and looking at  
22 hypertensive people, and the vast difference between  
23 the concentrations found in patients with heart  
24 failure and patients without heart failure.

25 As Dr. Manno had mentioned, it is not a

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1 stand alone test. You still have to look at the  
2 patient. I think we will provide information that  
3 will lead the physician in making a proper decision.  
4 I thank the panel for taking the time and FDA for  
5 reviewing this application.

6 DR. GUTMAN: It is my understanding you're  
7 going to go around and give us advice on how to  
8 proceed, those who voted supporting the nonapproval,  
9 and will explain to the company and to the agency how  
10 to get it right.

11 DR. KROLL: I think that is a good  
12 approach to take. Let me start with just a few  
13 comments. We've really focused a lot on the clinical  
14 aspects but there are a lot of technical aspects that  
15 have not been substantiated such as the true accuracy  
16 of this test. There's a lot of references to atorian  
17 literature but there's no studies that have been shown  
18 that link this current method with the other methods  
19 that are out there, particularly those that are quoted  
20 in literature and that's extremely important.

21 If you have experience with a lot of  
22 different protein assays, you know that sometimes you  
23 get an assay that doesn't have any decent correlation  
24 at all of what's out there. You have to be extremely  
25 careful. And it's not a question in terms of response

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1 but this is a suggestion that that documentation be  
2 there. Also there weren't studies for linearity or  
3 calibration verification.

4 DR. BRUNI: We have some of the data  
5 comparing it to the Shinogi test. We did not submit  
6 that because the Shinogi test is not a test that was  
7 recognized by FDA as being approved but I can provide  
8 those data.

9 DR. KROLL: Okay. My point is that it's  
10 sometimes helpful to provide that. When I set up an  
11 assay in my lab, I always try to look for some other  
12 place that I can go ahead and test that assay out as  
13 a comparison for accuracy.

14 I'll just address real shortly my comments  
15 that we saw serious deficiencies in terms of having  
16 appropriately age-matched groups for comparison and  
17 groups where both men and men, women and women, and  
18 maybe particularly other subgroups.

19 Plus, I heard there were several comments  
20 that it's a good test distinguishing people who have  
21 pulmonary disease and those with congestive heart  
22 failure, yet there was no data supporting that. I  
23 guess one point is if you're going to make a point  
24 that it's useful for a certain area or certain  
25 clinical entity or distinction to make, that you have

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1 to provide the data and the data should be fairly  
2 clear.

3 A good collection of data is extremely  
4 important even though you can analyze it many  
5 different ways. That's critical. Now, I'll open it  
6 up to the rest of the panel members. Actually, we can  
7 go around the room. Why don't we start on that side  
8 with Dr. Comp.

9 DR. COMP: It's hard to get good data on  
10 healthy elderly. I would recommend you look in the  
11 gymnasiums and fitness clubs. Maybe it will be to  
12 your benefit. They will be super healthy and they are  
13 usually very health conscience individuals. I think  
14 you could pick up your normal healthy folks there.

15 DR. PACKER: In addition to find the  
16 healthy people at the gymnasium, I suppose, I would go  
17 and find some normal -- normal is not a good word --  
18 some common-place old people who have other disorders.

19 Actually the best control group here are  
20 not healthy people but old people who come in who have  
21 a little hypertension, a little coronary disease, a  
22 little renal insufficiency, and who don't have heart  
23 failure and compare them to old people who have  
24 hypertension and coronary disease and renal  
25 insufficiency a little bit who do have heart failure

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1 because that's how physicians are going to use the  
2 test.

3 They don't want to know whether the person  
4 is healthy compared to a 40-year-old or even to  
5 another 70-year-old. They want to know if the person  
6 has heart failure compared to the same person without  
7 heart failure. That's what they want to know.

8 I would actually emphasize the collection  
9 of data in elderly patients with concomitant disorders  
10 but you don't have heart failure because I think that  
11 would be very, very important. I suspect that when  
12 you're looking at all the data, you may find that this  
13 is not a disease. This is not a test that easily  
14 distinguishes people with or without heart failure who  
15 are stable outpatients.

16 This might be a test that is ideally  
17 suited for the ER, or ideally suited to distinguish  
18 pulmonary disease from cardiac disease, or ideally  
19 suited to follow the affects of treatment  
20 sequentially. That would allow you to define the  
21 appropriate place of this particular test in the  
22 practice of medicine.

23 I strongly suspect, I can't say one way or  
24 the other, this is not a test that if you get a whole  
25 large amount of data in the elderly that you're going

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1 to find the cutoff that you'll be happy with that will  
2 distinguish people with your without heart failure.  
3 Probably a test that is much better suited to special  
4 situations.

5 DR. CLEMENT: Steve Clement. I concur  
6 with those comments. I think looking at the control  
7 group very carefully, screening them, using very  
8 careful physical exams, and possible other best  
9 measurements for looking at cardiac disease such as  
10 possibly an echo to make sure that they don't have  
11 heart disease but they do have other things. That  
12 would be a good way of getting a good control group.

13 DR. EVERETT: James Everett. What I would  
14 suggest is, first of all, you make sure your data set  
15 match a hypothesis. That is, it doesn't convince me  
16 when the Food and Drug Administration statisticians  
17 come in and, in a sense, do your work. That is, they  
18 actually age-match your data which should have been  
19 done before we got here.

20 That's the kind of thing that doesn't  
21 convince me when I look at the data set when you tell  
22 me you have age-matched controls and when I look at  
23 them they are not age-matched. If you don't think  
24 that's important, then don't say that. If you do,  
25 explain to me what you mean or explain it to anybody

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1 when a panel usually will contain a certain number of  
2 scientists.

3 The other thing about the stratification.  
4 the stratification is very strong and supported with  
5 any data set. It really tells you what other  
6 variables are in your data set. What are the  
7 things that makes whatever you monitor go up and what  
8 makes it go down. You don't have to stratify every  
9 little variable but at least if it's male and female,  
10 stratify the data based on male and female, whatever  
11 your major variables are.

12 I think if you stratify them, many of the  
13 questions that we asked would not have come up.  
14 Basically what I would like to suggest is that you  
15 just make sure your data set match your hypothesis  
16 because if it doesn't, it just opens up all kind of  
17 holes.

18 DR. MANNO: I agree with everything that  
19 has been said. One thing I would suggest is to get  
20 some idea if there's any change with renal function  
21 change since there's already reported data on the  
22 dialysis patients before and after dialysis. I would  
23 look at some of the older patients that have a little  
24 bit of impaired renal function but at the same time  
25 they don't need dialysis particularly.

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1 DR. BRINKER: I think you've heard pretty  
2 much where the deficiencies are in the data. Some of  
3 the data that wasn't available to us because it hasn't  
4 been in the PMA may answer some of these questions.  
5 I think if you look for a limited indication, you can  
6 have more focused data on something that you and the  
7 FDA can I think work out perhaps without the need for  
8 another panel meeting.

9 DR. HENDERSON: I have nothing to add.  
10 Thank you.

11 DR. ROSENBLOOM: Likewise.

12 DR. RIFAI: I just want to add one more  
13 thing. In the initial claim from the sponsor was this  
14 test was to be used to aid in the diagnosis and the  
15 management. Most of the studies, if not all the  
16 studies, were geared toward the diagnostic end of it  
17 and it was implied for management. I really believe  
18 that probably this test might have even more value in  
19 the management of these patients so perhaps this is a  
20 consideration you might have to address this  
21 particular issue.

22 DR. KROLL: Thank you. I would like to  
23 thank all the panel members. Dr. Gutman, is this  
24 sufficient for you?

25 DR. GUTMAN: Yes, this is fine. Thank

**NEAL R. GROSS**

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1 you.

2 DR. KROLL: I want to thank everyone else.  
3 I thank the sponsors for their presentations. I thank  
4 the FDA staff for all their assistance and help.

5 (Whereupon, at 4:00 the meeting was  
6 adjourned.)

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CERTIFICATE

This is to certify that the foregoing transcript in the

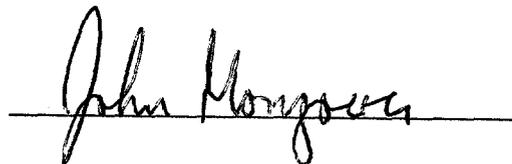
matter of:                   CLINICAL CHEMISTRY AND CLINICAL  
                                  TOXICOLOGY DEVICES PANEL

Before:                       MEDICAL DEVICES ADVISORY COMMITTEE

Date:                         MARCH 24, 2000

Place:                        ROCKVILLE, MARYLAND

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

A handwritten signature in cursive script, appearing to read "John Monaghan", is written over a horizontal line.