

1 C, does anyone have any concept of why the  
2 radiolucencies are so high in the acetabular cup?

3 DR. YASZEMSKI: Mr. Craig--and may I  
4 remind folks who come up to talk at the microphone  
5 to please introduce yourselves each time you step  
6 up.

7 MR. CRAIG: I am Tom Craig.

8 Basically, as far as the indications that  
9 went into the application, what we were intending  
10 was to include all the indications that you have  
11 for possibly a metal-on-polyethylene acetabular cup  
12 or a cemented/cementless stem, and not to  
13 artificially change the fixation methods of the  
14 total hip just due to the metal-on-metal  
15 articulation.

16 And we do have the clinician from Study C  
17 here. I would like to ask him to address the issue  
18 about the lucencies.

19 DR. LOMBARDI: Hello. My name is Adolph  
20 Lombardi, and I am from Columbus, Ohio. I am a  
21 consultant with Biomet.

22 I was involved in Study C as far as  
23 utilizing both the metal-on-polyethylene and the  
24 metal-on-metal device. In that study, I did 42 of  
25 those cases, and we had reported 7 cases of

1 radiolucencies around the metal-on-metal components  
2 and 5 cases around the metal-on-polyethylene.

3 I have brought some x-rays of those  
4 particular cases so that you can see that these  
5 radiolucencies are very minimal and nonprogressive  
6 and in several cases actually disappeared.

7 [Slide.]

8 This gentleman presented with degenerative  
9 joint disease of his left hip, as you see here,  
10 with significant disease, and he underwent the  
11 metal-on-metal arthroplasty.

12 [Slide.]

13 Here is his initial postop radiograph,  
14 which I believe does not show any evidence of any  
15 radiolucencies or gaps.

16 [Slide.]

17 Here is his one-year follow-up, which  
18 again I do not believe shows any migration or any  
19 evidence of any radiolucencies.

20 [Slide.]

21 At his 2-year follow-up, we caught this  
22 slight line here. Now, as part of my operative  
23 procedure, I like to use a slurry graft. This  
24 means I use reamings from the femoral head, and I  
25 put them down as a graft, and I don't know whether

1 this is a condensation of bone or truly a  
2 radiolucent line, but this is the type of  
3 radiolucent line that we were identifying.

4 [Slide.]

5 Here is the 4-year follow-up, and again, I  
6 don't believe I see it there.

7 [Slide.]

8 And then, a 5-year radiograph on this  
9 particular patient.

10 That was the typical radiolucent line that  
11 we were calling in the metal-on-metal.

12 DR. FINNEGAN: Okay. My second question  
13 has to go to metal ion toxicity, which I think  
14 really is a different animal than polyethylene  
15 debris. Two points. One is can anyone address  
16 titanium ions, because certainly in other implants,  
17 that has been found to leach out, and it also  
18 appears to have much more cellular toxicity than  
19 the cobalt for sure. And what--I don't know  
20 exactly how to phrase this question--but how  
21 uncomfortable would people be with a registry for  
22 younger patients that go out 10 years with the same  
23 implant and having them evaluated for particularly  
24 the hematopoietic cancers?

25 MR. CRAIG: Thank you.

1 I am not going to be able to answer the  
2 toxicity questions, but as far as the design that  
3 is in the petition, I think they need to make it  
4 clear that the articulating surface that we are  
5 talking about is cobalt-chrome/cobalt-chrome. We  
6 have titanium in the petition as an acetabular  
7 cut-backing and as a femoral stem, but the  
8 articulation surface itself is only  
9 cobalt-against-cobalt.

10 Dr. Jacobs, did you want to try the  
11 others?

12 DR. JACOBS: Thank you.

13 Josh Jacobs from Rush Medical College.

14 The issue of titanium ions is one that we  
15 have studied extensively. I don't know that I  
16 would agree with your premise that they are more  
17 toxic or cellularly active--I forget the exact  
18 phrase you used--than cobalt-chrome debris.

19 Some of that information comes out of  
20 comparative studies that have looked at particulate  
21 titanium and particulate cobalt-chrome, showing  
22 that at certain dose levels, the titanium debris  
23 tends to elicit more inflammatory cytokines, such  
24 as isle-1 [phonetic] and TNF-Alpha.

25 But part of that reason is because

1 cobalt-chrome is actually toxic at the  
2 concentrations used. These are cell culture  
3 studies, typically given bolus doses not  
4 necessarily representative of what happens in situ,  
5 which is a smaller dose over a longer period of  
6 time. So in fact if you get the cobalt-chrome dose  
7 down low enough, it has a similar type of  
8 inflammatory mediator profile in terms of secretion  
9 from macrophages.

10 We have measured elevations of serum  
11 titanium in patients with well-functioning total  
12 joint replacements. We have not measured them in  
13 patients who have metal-on-metal bearings, although  
14 that is a potential source if you have fretting at  
15 the metal junctions. If you have a well-designed  
16 couple, however, and if it is carefully tested, the  
17 potential for fretting can be minimized.

18 So I don't think that, at least on the  
19 metal-on-metal bearings that are the subject of  
20 this petition, which are all based on cobalt-chrome  
21 bearing surfaces, that titanium toxicity is a major  
22 issue.

23 In terms of the registry for younger  
24 patients, that is a wonderful idea. As a matter of  
25 fact, we have been bandying this about in the

1 Academy, as you know; we have been talking about  
2 setting up a joint replacement registry not only  
3 for younger people but for older people. Such a  
4 registry exists in many of the Scandinavian  
5 countries; they can do it because of their system  
6 of government. But I would like to remind you that  
7 even with the Scandinavian registries that have  
8 been brought to bear with this problem, both the  
9 Swedish and the Finnish registries, and in some of  
10 the data, I think, from the Danish registry as  
11 well, we still have been unable to answer the  
12 questions.

13           And number two, in the United States, the  
14 hurdles to establish some kind of registry are  
15 substantial in terms of, number one, medical/legal  
16 issues, liability issues, in view of the Freedom of  
17 Information Act; and number two, and perhaps even  
18 more of an obstacle, is the patient privacy  
19 initiatives that are going on.

20           DR. FINNEGAN: I am looking at something  
21 probably more like a surveillance tool than  
22 actually a formal registry such as in the  
23 Scandinavian countries.

24           DR. JACOBS: Yes. In order to get at  
25 these basic questions, you need something like a

1 registry, something like a formal registry, to try  
2 to capture all the patients. I think this is  
3 something that is probably out of the scope of the  
4 FDA. This is something that I think has to be done  
5 on a Congressional level to provide the protections  
6 that are needed against unwanted incursions into  
7 the database to provide the protections to the  
8 patients, et cetera.

9 In the current political environment, I  
10 don't know that that is a feasible endeavor without  
11 further legislation.

12 DR. FINNEGAN: But you all would  
13 participate.

14 DR. JACOBS: Yes, sure.

15 DR. YASZEMSKI: Thanks, Dr. Finnegan.

16 Thank you, Dr. Jacobs.

17 May I ask for Dr. Lyons' comments?

18 DR. LYONS: Yes. I was actually quite  
19 intrigued by the materials. There were quite a lot  
20 of background materials to review through, and I  
21 had a favorable impression from an engineering  
22 standpoint on the bearing surface itself.

23 I, however, would echo some of the  
24 comments that were brought up earlier about the  
25 testing and the testing design and its latitude,

1 because the design here is a little bit different  
2 than just metal-on-polyethylene. There is a "poly  
3 buffer," if you want to call it that. I would be  
4 interested to know about the loading and the change  
5 of implantation issues that might come up in  
6 practice because not all the surgeons are exactly  
7 the same in terms of optimal positioning and skill.

8           And it may be more of a rhetorical  
9 question, but whether the testing that has been  
10 proposed is actually going to be sufficient to  
11 address some of the change in design of this  
12 particular device where it has the poly lining.  
13 I'm thinking of creep and some of the other issues.  
14 I think that was already brought. I don't know if  
15 there is someone who does have a little more  
16 insight into why they think the testing is  
17 sufficient. That would be one point that I would  
18 be interested in.

19           The other point I would echo is the  
20 follow-up; I think that to watch for  
21 carcinogenicity and some of the other issues will  
22 just take a lot of time to follow up, but I do see  
23 the advantages to low wear debris, and some of the  
24 results from the McKee-Farrar over time are quite  
25 impressive, and if we are considering that we are

1 going to eliminate some of the scatter given the  
2 design change, I would be more comfortable, since  
3 we don't have long-term clinical follow-up, if our  
4 testing and simulation were actually  
5 well-thought-out covering these issues.

6 DR. YASZEMSKI: Comments from Petitioner?

7 MR. CRAIG: Yes. Basically, the issues  
8 that you are raising as far as wear testing, in the  
9 testing that was presented a little while ago of  
10 the metal-on-polyethylene and that sort of thing,  
11 those are somewhat dated study. There is a lot  
12 going on in wear testing today, as we speak, and  
13 the testing that is being done is much, much better  
14 than it was in that period of time.

15 As far as testing in a nonoptimal position  
16 and that sort of thing, that would depend to some  
17 extent on the design. I would like to bring Dr.  
18 Frank Chan up, who has done wear testing and is  
19 familiar with his design and can probably address  
20 what would happen if you did it somewhat slightly  
21 off-axis.

22 DR. MEDLEY: I'm a last-minute substitute;  
23 I am not Frank Chan. I am John Medley from the  
24 University of Waterloo.

25 The wear testing issues--I am not so

1 sure--I could be wrong about this--but I don't  
2 think the poly sandwich was part of our petition.  
3 I think our petition just had metal, a metal shell  
4 or taper-lock [phonetic] shell. So many of those  
5 issues would go away if it is not in our petition.

6           On the issue of some of the kinematic  
7 details and different angles, there is not much  
8 data on this. We proposed once to study it for  
9 ceramic-ceramic, and we haven't completed that yet,  
10 but there has been some work at Leeds where they  
11 changed the kinematics of their simulator to allow  
12 the paths to come up closer to the edge, which was  
13 somewhat similar to the idea of not having it quite  
14 of the same orientation. When they did that, they  
15 got an increase in wear but not a dramatic  
16 increase; in fact, some of the data where they did  
17 that--I was going to say it was going to say it was  
18 on my graph, but it wasn't, because it was as later  
19 study--but it was not out of line with the data  
20 that was on my graph looking at simulator compared  
21 to clinical.

22           Does that cover what you asked?

23           DR. LYONS: One of my issues, to get right  
24 to the edge, would be the boundary condition in  
25 impingement. That would be the concern that I

1 would have. In the ceramic--just to take an  
2 example there--to protect the ceramic, the  
3 geometries can be changed so that there isn't  
4 impingement to cause cracking. But here, you are  
5 talking about metal-metal impingement issues, and I  
6 didn't know if that was studied as well as  
7 optimally could be done.

8 DR. MEDLEY: I don't think it has been  
9 studied. I don't think--although I can't prove  
10 this--that metal-metal would be quite a sensitive  
11 as ceramic-ceramic to the impingement issues. But  
12 there could be a problem with it, and as far as I  
13 know, there has been no simulator testing that has  
14 directly looked at that. There is some recent data  
15 from Leeds that I believe, as I said, the  
16 kinematics brings the contact closer to the edge  
17 just by the way they run their simulator, and there  
18 may even be some where they looked at different  
19 angles, but I can't recall for certain.

20 DR. LYONS: That was just one of the areas  
21 that I was interested in for the impingement, then  
22 the leverage, the loosening, those kinds of  
23 problems that could occur with suboptimal  
24 implantation. It's just a question.

25 DR. MEDLEY: I don't have any direct data

1 to add to that from a simulator testing point of  
2 view.

3 DR. YASZEMSKI: Mr. Craig, could I ask you  
4 to comment on whether the polyethylene sandwich is  
5 included or is not included in the petition?

6 MR. CRAIG: Absolutely. Basically, I  
7 think the only inclusion of the polyethylene  
8 sandwich is in the literature. I think that is  
9 restricted to the Sulzer design, and the two  
10 designs that were part of the study that the data  
11 was presented in the petition did not have  
12 polyethylene.

13 DR. YASZEMSKI: So for clarification,  
14 then, the proposal for reclassification does not  
15 include that?

16 MR. CRAIG: I would say that that would  
17 not exclude that, simply from the standpoint that I  
18 think the Sulzer design with the polyethylene--and  
19 FDA can correct me if I'm wrong--was the first  
20 cleared metal-on-metal hip, and it is currently  
21 available in the U.S. today; and we would like to  
22 cover that as well, if we can.

23 DR. YASZEMSKI: Okay. Thanks very much,  
24 Mr. Craig.

25 Let's now ask Dr. Wright for comments.

1 DR. WRIGHT: No questions.

2 DR. YASZEMSKI: No questions from Dr.  
3 Wright.

4 Dr. Cheng?

5 DR. CHENG: Well, I found reviewing the  
6 materials that my mind swung back and forth on the  
7 issue of whether or not to reclassify this device.  
8 I thought it was a very difficult in my own mind to  
9 come to some meaningful conclusion, partly because  
10 I really hope for a better prosthesis myself so  
11 that when I reach the age at which I might need a  
12 hip replacement, I know what is best for  
13 myself--and everyone else--of course, that would be  
14 in the best public interest.

15 So I think there is a lot of work that has  
16 been done and presented to us already this morning.  
17 One of the problems, I think, with the polyethylene  
18 experience, the metal-on-polyethylene articulation,  
19 has been that over the years, we have gone around  
20 in circles at meetings looking at different  
21 problems, trying to solve one problem and instead  
22 begetting another one that perhaps we didn't  
23 anticipate. And many questions remain unanswered.

24 I think that presently, the industry and  
25 the FDA are doing a much better job, perhaps in the

1 last 5 or 10 years than 20 or 25 years ago, in  
2 terms of doing studies, trying to answer the most  
3 important questions; the studies are  
4 better-designed, they are statistically analyzed  
5 better, they are better controlled, and there are  
6 better outcomes instruments with which to measure  
7 any differences that may be present.

8           So in my own mind, just from the summary  
9 of the data that was presented, if I were to look  
10 at whether or not the metal-on-metal articulation  
11 has enough justification to reclassify, and you  
12 compare that to the metal-on-polyethylene  
13 experience, I would probably say there is probably  
14 similar data on both--however, I worry and am  
15 concerned that if that were to occur, we would  
16 recapitulate the experience with the  
17 polyethylene-metal articulation, and there would be  
18 a lot of questions that would remain unanswered.  
19 It would create perhaps more problems; there would  
20 be more devices out. So I'm not sure that that is  
21 in the public interest.

22           If we do not reclassify it, it creates a  
23 tremendous burden on the manufacturers and on the  
24 FDA to get a much larger amount of work done, a  
25 much larger control--the manufacturer [inaudible]

1 the FDA with a Class II device has a fair amount of  
2 control to regulate the device in regard to the  
3 risks that have been presented, but with a Class  
4 III device, there is even more control over that.

5           So I guess if I were to stand here and  
6 look at the public interest, which is I guess what  
7 I am supposed to do on this committee, I think the  
8 burden will be greater on the FDA and on the  
9 manufacturers to continue to keep this in a Class  
10 III classification, but I think more questions 20  
11 years from now will be answered--we will be able to  
12 give answers more confidently--and for that reason,  
13 I think it is probably too early to consider a  
14 reclassification at the present time. I just don't  
15 think we'll make as much progress, and it won't be  
16 in the public interest to do that right now.

17           DR. YASZEMSKI: Dr. Larntz, you presented  
18 already your statistical review. Do you have any  
19 other either comments or, specifically, thoughts on  
20 your answers to any or all of the three questions?

21           DR. LARNTZ: I just want to ask the  
22 sponsor the question that I posed in my  
23 presentation, which is were the values presented in  
24 the graphs just simple means of different numbers  
25 of patients through time. That's a simple

1 question, and I'd just like to have the answer to  
2 that.

3 DR. YASZEMSKI: Would anybody from the  
4 Petitioner like to address that--and again, I'll  
5 remind you to please state your name, affiliation,  
6 and any financial interests.

7 MR. VOORHOST: My name is Paul Voorhost.  
8 I am employed by DePuy Orthopedics; I am a  
9 biostatistician there, and I put together the  
10 information that you have reviewed.

11 The answer to the question is that those  
12 are simple means. They are plotted in the actual  
13 N's, means, and standard deviations.

14 DR. LARNTZ: So there are different  
15 numbers of patients at each time point, and so on.

16 MR. VOORHOST: There are.

17 DR. LARNTZ: So, no longitudinal  
18 adjustment or anything across time so far?

19 MR. VOORHOST: There is not, and if I  
20 could just briefly explain why I didn't do that--I  
21 think it was pointed out previously that  
22 historically, the FDA is interested in a minimum of  
23 2-year follow-up. In the data that we analyzed, I  
24 think there were about 30 cases that had  
25 information at 3 years and maybe 10 at 4 years, so

1 it didn't really lay out very well for doing a  
2 longitudinal analysis at that point.

3 DR. LARNTZ: But there were also 6-month  
4 and 6-week and pre-op and one year. I mean, it  
5 sounds like there is a lot of data through time.

6 MR. VOORHOST: There is. That is true.

7 DR. LARNTZ: And it seems like a lot of  
8 data through time would lend itself to longitudinal  
9 analysis. I'll stop there. You don't have to  
10 answer.

11 I have no further comments.

12 DR. YASZEMSKI: Thank you, Dr. Larntz.

13 Mr. Dacey, may we ask if you have any  
14 comments or input from a consumer perspective?

15 MR. DACEY: Every time I approach a  
16 subject such as this, of course, I always take it  
17 from the perspective of what does this mean to the  
18 patient. And this is an area where I do have a  
19 little bit of experience, but I'll get to that in a  
20 moment.

21 After reviewing all the material--the 20  
22 pounds of paper that I received--the one question  
23 that occurred to me--and it is a question that I  
24 cannot answer; the panel can answer it, I hope--the  
25 overriding question that came up was how much has a

1 scientific body of knowledge regarding the efficacy  
2 and safety changed, improved, to justify  
3 reclassification from III to II? Again, I can't  
4 answer that personally. But also, I started  
5 looking for new evidence to support and clarify,  
6 and of course, I had a little trouble finding  
7 really new evidence, and I saw the need for the  
8 long-term prospective studies that come along.

9           Three times a week, I go--because I have a  
10 prosthetic leg--and work out in a therapy pool, and  
11 I have counseled a lot of patients over the years,  
12 and I see in that therapy pool a great many total  
13 hips. And I have to acknowledge the younger  
14 patients approach their rehab very aggressively,  
15 with an eye toward getting back to normal function  
16 as quickly as possible--and beyond. And then, of  
17 course, I see some seniors, older patients, who  
18 have a great deal of difficulty.

19           So there are two different curves at work  
20 there, and I sure, from a patient perspective, like  
21 to see those two different curves--which segues  
22 into the whole patient information area. On the  
23 other panel I serve on, I am constantly talking  
24 about patient skill training, not just information  
25 and education, and I suspect that this is an

1 intervention that again goes beyond what we have  
2 done--and a lot of the burden, of course, falls on  
3 the physical therapist--but I see the skill  
4 training issue as one that has to be  
5 demographically looked at. It certainly has a  
6 different tilt for that younger patient who wants  
7 to go back and run marathons than for the patient  
8 who just wants to be able to shop comfortably at  
9 Wal-Mart.

10 So in summary, all I can say is that I  
11 personally cannot see how much the body  
12 acknowledges change, so I have to rely upon you to  
13 tell me so that I can in turn, when I see patients  
14 and interact with them, hopefully give them some  
15 levels of confidence that I can't right now.

16 DR. YASZEMSKI: Thank you, Mr. Dacey.

17 Ms. Maher, the industry perspective.

18 MS. MAHER: From an industry perspective,  
19 I'd like to remind the panel that all of the  
20 metal-on-metal devices that are currently on the  
21 market were cleared through the 510(k) process,  
22 which is the same process that they will be going  
23 through or would be going through if we  
24 down-classify them to Class II, which indicates  
25 that the information that is currently available

1 and the controls that are in place have, at least  
2 until now, been deemed to be sufficient to  
3 demonstrate that the products will be safe and  
4 effective for their intended use. That is just one  
5 thought that I'd like to make sure everybody  
6 remembers, that all the metal-on-metal products  
7 that are in use in the United States right now--and  
8 the FDA had a slight that said six; I think I know  
9 of four--have been cleared through the 510(k)  
10 process.

11           The other thing I would like to comment on  
12 or actually ask the sponsor to throw some  
13 information up on the slides is that the FDA  
14 presentation indicated a fairly low follow-up rate  
15 on the patients. I know that in the panel booklets  
16 that we got, there was the third amendment that  
17 included information on the patients who had not  
18 been ready for follow-up at the time. I think it  
19 would be very interesting to see how the rates  
20 changed when they throw that information up.

21           Thank you.

22           DR. YASZEMSKI: Thank you.

23           Mr. Craig, would you like to comment on  
24 Ms. Maher's question?

25           MR. CRAIG: Yes, thank you.

1           You are absolutely right on that, Sally.  
2   The petition that was put together that you got in  
3   the May date was actually based on response to  
4   questions from FDA, and it reflected a database  
5   that was active at that point in time and a number  
6   of patients who had gone into the 24-month time  
7   interval, many of whom had not cleared the 24-month  
8   time interval.

9           So Studies A and C were still ongoing, and  
10   that made it appear like there was a low level of  
11   follow-up. Now, Study B was a study that was  
12   conducted in Europe to European standards, and  
13   that, we could not do anything with. But we did  
14   try to address Studies C and A in the submission  
15   that you got just a few weeks ago in that little  
16   blue book, and I'd like to get Steve Wentworth to  
17   come up and talk about that.

18           MR. WENTWORTH: Steve Wentworth, Clinical  
19   Research at DePuy, and my interest in this petition  
20   is that it allows me to eat.

21           [Slide.]

22           I just have a couple slides. As Tom  
23   alluded to when we submitted the petition back in  
24   March of 2000, the database had actually been  
25   locked earlier than that, and a lot of the patients

1 had not progressed into or very many beyond the  
2 24-month interval. And I am not exactly clear, and  
3 perhaps Glenn can explain to you how they  
4 calculated the percentages of follow-up compliance  
5 at those different intervals.

6 But if you look at this slide, it shows  
7 the metal-on-metal cohort of patients. At the time  
8 that the database was locked, we had 105 patients  
9 who were within the 24-month interval; we also had  
10 49 patients who had gone beyond the 24-month  
11 interval. And of those 105, we had 65 who were  
12 seen since the database was closed, or they had a  
13 known status. So we had a total of 68 patients of  
14 those 105 who had been seen or had a known status,  
15 i.e., a phone call, a not back from the patient  
16 that their condition was fine. Of the 49 who were  
17 past due, we received an additional 9 cases of  
18 those past due who had moved beyond the 24 months.  
19 They had either come back later at a follow-up  
20 interval and were in fact rolled back into the  
21 24-month interval, or an evaluation had just not  
22 been received from the clinical investigator. So  
23 we had 9 of those and we had another 3 that we knew  
24 their status at the time.

25 So if you look down there at the bottom,

1 in the metal-on-metal cohort, 80 were seen or had a  
2 known status since the database was locked, and  
3 that brings the follow-up compliance rate up to  
4 79.6 percent, pretty close to 80 percent. So  
5 that's a much improved follow-up compliance than  
6 what FDA had projected previously.

7           Then, if we look at the  
8 metal-on-polyethylene, you will see the same kind  
9 of things. We had 70 at the time who were not yet  
10 overdue, we had 40 who had come back since then,  
11 and another 4 that we knew the status of. Past  
12 due, we had 11, and we had 5 that we got  
13 evaluations back subsequent to that, and 2 more of  
14 those 11 that we had a known status.

15           You'll notice down here that that brings  
16 the compliance level up substantially for the  
17 metal-on-polyethylene group to 93.1 percent, which  
18 is very, very good, I think, in anybody's  
19 estimation.

20           And then, just let me point out that the  
21 reason why the compliance is so much better is  
22 because if you recall, Study B was an open study;  
23 there were no metal-on-polyethylene patients to be  
24 reported on, plus, as Tom Craig alluded to, that  
25 study had been completed in Europe. It was really

1 designed more as a short-term safety study. So  
2 that study was over, and we were not going to get  
3 any of those patients back. Obviously, I would  
4 think they would still continue to be seen by their  
5 clinicians, but the clinicians were not going to do  
6 the evaluations and take the x-rays and send them  
7 back to us, so that's why we have a slightly lower  
8 percentage there.

9 DR. LARNTZ: Could I follow up?

10 DR. YASZEMSKI: Yes, please.

11 DR. LARNTZ: Directly to these slides, do  
12 you have the follow-up for A and C alone--I mean,  
13 you put B in there, and it was obvious that you  
14 aren't going to get any improvement--but do you  
15 have the compliance, because it is very concerning  
16 if you have 93 percent on metal-on-polyethylene and  
17 a lower number on metal-on-metal. That says there  
18 is something wrong. So what is the A and C  
19 combined for metal-on-metal--do you know? Does  
20 anyone know?

21 MR. WENTWORTH: The A and C  
22 combined--excluding Study B?

23 DR. LARNTZ: Well, that's what you have  
24 for metal-on-polyethylene, isn't it? I'm sorry--am  
25 I mistaken?

1 MR. WENTWORTH: No. That's correct.

2 DR. LARNTZ: So the comparable number for  
3 A and C, I'd like to know for metal-on-metal.

4 MR. WENTWORTH: We could calculate that.  
5 I don't have that number of the top of my head.

6 DR. LARNTZ: Because if they are  
7 differential rates, that raises real questions.

8 MR. WENTWORTH: Again, it was really  
9 because of the status of the study that you have  
10 the disparity. We can get answer later.

11 DR. LARNTZ: Okay. Could we ask Mr.  
12 Craig--do you have it now--otherwise, we'll ask for  
13 it after lunch.

14 MR. CRAIG: Yes, I think that's actually  
15 in this blue book that you got, and I'll ask Paul  
16 Voorhorst to address that.

17 MR. VOORHORST: I don't have Studies A and  
18 C combined, but I have them separately.

19 DR. LARNTZ: Okay, that's fine.

20 MR. VOORHOST: For the metal-on-metal  
21 treatment group in Study A, the follow-up rate was  
22 87 percent. And for Study C in the metal group,  
23 the follow-up compliance was 76 percent, and that  
24 does not include adding in those patients who were  
25 seen subsequent to the database lock.

1 DR. LARNTZ: Okay.

2 MR. VOORHOST: Those are the compliance  
3 numbers that represent the data analysis in the  
4 petition.

5 DR. LARNTZ: No--I'm just asking for the  
6 follow-up ones, the ones that are the follow-up;  
7 and I think you can calculate those later and give  
8 us those.

9 MR. VOORHOST: I've got those now, too, if  
10 you'd like. When you roll in those patients who  
11 were seen since the database lock--

12 DR. LARNTZ: Right; they correspond to the  
13 93. I want to see what the number is that  
14 corresponds to the 93--comparable number.

15 MR. VOORHOST: All right. In Study A,  
16 that number is 94 percent, and in Study C, that  
17 number is 85 percent.

18 DR. LARNTZ: Thank you.

19 DR. YASZEMSKI: Thanks very much, and  
20 thanks, Dr. Larntz.

21 As we come around, may I ask Dr. Witten,  
22 have you any comments you might want to enter at  
23 this time?

24 DR. WITTEN: Just that--we had a different  
25 calculation from their subsequent information of

1 what the follow-up rates are, and unfortunately, we  
2 don't have a backup slide for it, but I think this  
3 is an optimistic version of their follow-up in the  
4 study.

5 DR. YASZEMSKI: Thank you, Dr. Witten.

6 Dr. Aboulafia.

7 DR. ABOULAFIA: I'll try to limit my  
8 comments to three things. The first is the  
9 information that Dr. Li presented in the  
10 preclinical studies and the concerns that I have  
11 about metals, that the classification allows for  
12 all metals. No mention was made about cast or  
13 wrought iron. Again, the titanium issue that was  
14 brought up--the manufacturer stated that the  
15 first-generation metal-on-metal problems, some of  
16 those problems were identified because of certain  
17 metals that were used or because of threaded cups,  
18 yet the petition doesn't try to exclude what the  
19 Petitioners identify as being problems to start  
20 with.

21 And then, the big issue about non-ideal  
22 testing, that the testing modes that were used  
23 were, again, under ideal circumstances, and we  
24 don't know how particulate debris and wear will be  
25 affected by non-ideal conditions. Those are real

1 issues that remain for me.

2           In terms of carcinogenicity, I think it  
3 has been addressed as well as can possibly be  
4 addressed in our lifetime by looking at  
5 Scandinavian registries. My only comment on it,  
6 because it is one of my areas of interest, looking  
7 at tumors, and I think the Petitioner has  
8 adequately addressed that issue, is that that  
9 relates specifically to overall risk and Question  
10 Number 1.

11           My biggest concern, though, is with the  
12 clinical information, which I think is terribly  
13 lacking. Specifically, despite the more optimistic  
14 follow-up that is presented under Tab 5, the data  
15 that is submitted in the first book, the orange  
16 book, identifies follow-up rates for Studies A and  
17 C of 37 and 47 percent in the investigational group  
18 and in the control group, 46 and 56, respectively.

19           Then, when they look at complication  
20 rates, those complication rates are calculated with  
21 a denominator of those patients who were originally  
22 enrolled in the study on the basis of intent to  
23 treat. So the more patients who drop off, the  
24 lower your complication rates, and there is a  
25 difference between the investigational group and

1 the control group, which would actually magnify  
2 those differences.

3 Taken to the extreme, if you lost all of  
4 your patients to follow-up, your patients would  
5 look perfect, and there would be no problems.

6 Then, when you look at revision rates of  
7 1.3 to 0.3 percent as seen on page 44, and  
8 calculate a difference of greater than 10 percent  
9 in follow-up, and that is an absolute percent  
10 difference, those differences are very powerful and  
11 more powerful than might meet the eye if one  
12 doesn't take that into consideration.

13 Then, just ultimately, a follow-up study  
14 with less than 50 percent of patients for a total  
15 joint study I think is at best poor.

16 Those are my concerns.

17 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

18 Dr. Peimer?

19 DR. PEIMER: Thank you.

20 Most of the comments I would make have  
21 already been emphasized. I was troubled by the  
22 submission that included designs that had clearly  
23 failed in the past and diameter-sizing with  
24 equatorial impingement that was not excluded and  
25 could have been. I guess I don't understand the

1 rationale for including something that we know  
2 doesn't work, and I think it is troubling when that  
3 kind of thing gets in and isn't limited before we  
4 have to say if we are going to approve it that it  
5 should be limited.

6 I would emphasize my belief and experience  
7 that aberrant physical situations in simulator  
8 testing are useful, and although they are not  
9 always telling, they can be of added information.

10 I didn't understand a point in the  
11 discussion that just came up at the microphone.  
12 After the database lock--I just want to make sure  
13 that I do understand--after the database was  
14 locked, the past dues were recorded by what method?  
15 Were they examined and x-rayed, or was this a phone  
16 call check-in; and if an examination was conducted,  
17 was it the treating/evaluating physician who did  
18 the examination and x-rays?

19 MR. CRAIG: First of all, the  
20 characterization of A and C in the May submission  
21 as having 50 percent loss to follow-up is a little  
22 bit troubling, because what this really is is a  
23 snapshot in time of the reporting of patient data  
24 with people still in that interval waiting on the  
25 surgeon to evaluate them, plus get the paperwork

1 back to the company, get the paperwork into the  
2 database, do the analysis. So it is not unusual  
3 for anybody conducting a study to have a time lag  
4 on this. That is why, when we locked the database  
5 at the time that we submitted the May submission,  
6 it had a high number of patients who were either  
7 past the 24 months, which we had the data on for  
8 the most part, or were actively in the 24 months,  
9 which would be a large number of patients because  
10 you are accruing faster as you conduct the study  
11 longer.

12           That is what Steve was trying to address  
13 on the ones that were locked and came back and got  
14 the data in at a later point in time; the ones that  
15 were addressed by methods other than actually  
16 getting the data back were very, very small.

17           DR. PEIMER: Right; and you indicate in  
18 your letter that--what I am asking is how those  
19 last datapoints were collected. So was it  
20 physician exam and x-ray, and if so, who was the  
21 physician who examined?

22           MR. WENTWORTH: Yes--when it says  
23 "received after database lock," those were case  
24 report forms for clinical and x-ray evaluations  
25 done by the clinical investigators in the study.

1 So we actually had the data report forms that would  
2 be entered into the database.

3 DR. PEIMER: Thank you.

4 And then, just overall philosophically, I  
5 want to agree with Mr. Dacey, who says that we are  
6 condemned to repeat history if we don't remember  
7 it. I think that is always a good principle.

8 Maybe from a personal perspective, during  
9 lunch, I can get Professor Medley to comment on the  
10 lingering LeBatt controversy.

11 Thank you.

12 MR. CRAIG: May I comment on the designs  
13 that are in the petition, because we are not  
14 petitioning to bring the Ring and the old designs  
15 back in.

16 DR. PEIMER: But isn't that left in?

17 MR. CRAIG: No.

18 DR. PEIMER: No.

19 MR. CRAIG: No. That is why we--

20 DR. PEIMER: So that is my  
21 misunderstanding.

22 MR. CRAIG: That is why we put the data in  
23 about the congruency and the surface finish and all  
24 that, and we are specifically not looking for the  
25 peripheral contact; we are limiting it to designs

1 that do not have the peripheral contact, that only  
2 have the apex contact. And when we got into  
3 discussions on trying to use that data that gives  
4 the range of sizes for it and the clearance on the  
5 hips, that is not to say that some future design  
6 couldn't fall outside that range and yet be  
7 demonstrated to be substantially equivalent, which  
8 is why we propose the wear testing mechanism as a  
9 clearing mechanism versus a design-tied-in  
10 mechanism.

11 DR. PEIMER: But wear testing isn't going  
12 to necessarily give you equatorial contact failures  
13 from dislocation during normal use or jogging or  
14 playing tennis.

15 MR. CRAIG: That's one of the difficulties  
16 with trying to deal with this, yes, but that is why  
17 we also had the data in there to preclude the  
18 equatorial contact.

19 DR. PEIMER: Thank you.

20 DR. YASZEMSKI: Thank you.

21 Dr. Skinner, you have presented. Have you  
22 any other comments as we come around to you?

23 DR. SKINNER. Yes. I'd like to ask a  
24 couple questions just to put a couple things to  
25 bed.

1 First of all, on the issue that we were  
2 just talking about, I'd like to ask Professor  
3 Medley--the data that was sent to us included  
4 diametrical clearance, sphericity, surface  
5 roughness. I was particularly worried about the  
6 diametrical clearance. It would seem to me that it  
7 would be better to present this data or to limit  
8 the sizes of the cup and the head in terms of the R  
9 equivalent. You used the R equivalent  
10 term--basically, what the radius would be of a ball  
11 on a flat surface--I thought.

12 DR. MEDLEY: Yes, I used both. In fact,  
13 we had debates about this. To my mind, the  
14 effective radius is a neater way to present it. It  
15 combines both the size and the clearance. So  
16 whenever we mentioned clearance, we would also  
17 mention the diameter. So we mentioned that  
18 clearance range of 30 to 200 micrometers for a  
19 28-millimeter implant.

20 The reason we didn't put in the effective  
21 radius as the parameter is because it is not widely  
22 recognized in industry or by the surgeons. The  
23 clearance is the one that is most often talked  
24 about. And I have presented papers where I have  
25 presented the effective radius concept, and yet

1 they continue to talk about clearances and  
2 diameters, so-- they are equivalent; it is just  
3 that clearance and diameters together is a clumsier  
4 way of presenting that kind of data.

5 DR. SKINNER: My concern is that next  
6 month, Zimmer decides to have a 30-millimeter  
7 head--how does that change that--or a 35-millimeter  
8 head, or a 48-millimeter head. Are the clearances  
9 going to be the same? Probably not.

10 DR. MEDLEY: No.

11 DR. SKINNER: But the effective radius  
12 isn't going to change.

13 DR. MEDLEY: No, no. To maintain the same  
14 effective radius, you would have an increase in  
15 clearance as your radius increased. That is  
16 sometimes called reduced radius, sometimes  
17 effective radius. That effective radius relates  
18 directly to lubrication and to contact, the size of  
19 the contacts when you put the two into contact.

20 DR. SKINNER: So, to put you on the spot,  
21 should it be effective radius, or should it be  
22 clearances?

23 DR. MEDLEY: If it is going to be  
24 clearances, it has to be clearances plus diameter,  
25 so you would have to define the range with the

1 clearance and the diameter at each end, or you  
2 could never mention clearances alone without the  
3 diameter or the radius.

4           It could be effective radius alone, and it  
5 would require a bit of broad education as to how it  
6 worked. So it is sort of a semantic issue, but  
7 they can be made equivalent. It is just the  
8 clearance plus the diameter is to my mind just a  
9 slightly clumsier way of doing it.

10           DR. SKINNER: I've got a couple more  
11 questions--not for you.

12           Dr. Jacobs, I don't know, Josh, if you  
13 have heard about the cardiomyopathy associated with  
14 cobalt that was reported in the internal medicine  
15 journals in the sixties. My question is do you  
16 think it would be unreasonable to put a relevant  
17 contraindication in the labeling for alcoholics?

18           DR. JACOBS: Yes, I am familiar with the  
19 cobalt-beer-cardiomyopathy story, and that is why I  
20 only drink very fine wines--no.

21           [Laughter.]

22           That was I think an idiosyncratic event.  
23 I don't know that such a situation has been  
24 reported with other alcoholics of cardiomyopathy  
25 associated with large beer consumption. I think

1 that that was just something that was unique to  
2 that part of the world.

3           So I don't think you need to consider  
4 changing the indications for individuals who are  
5 alcoholics. On the other hand, I think the issue  
6 of comorbidities that was brought up is an  
7 interesting one. If you have someone who has renal  
8 failure, that may be a situation, because in the  
9 setting of renal failure, you are not going to  
10 clear the metal as efficiently, and in the setting  
11 of chronic renal failure, that may be a relative  
12 contraindication--and I say "relative  
13 contraindication" for some of these devices that  
14 generate high amounts of metal debris.

15           DR. SKINNER: One more question for Dr.  
16 Schmalzried. There are two questions. First, in  
17 the study group, there were an awful lot of  
18 perforations and dislocations in the intraoperative  
19 dislocations. That is one question. Do you have  
20 any comments on why that might be? I mean, the  
21 people putting these things in are pretty confident  
22 surgeons.

23           The second question is are you familiar  
24 with the article by Weber and Core in 1996 where he  
25 described one case of extraordinary wear, whereas

1 most of his patients had 4 to 6 microns per  
2 year--100 hips, 3-1/2-year follow-up.

3 DR. SCHMALZRIED: The second one, I'll  
4 take first, because that's easy. The answer is I'm  
5 not familiar with that and would ask you to tell me  
6 what his definition of "extraordinary wear" is.

7 This issue of runaway wear with  
8 metal-on-metal hips comes up, and I am always  
9 curious as to the origin of that and what the  
10 definition is of "runaway" or "excessive," because  
11 as somebody who has been doing implant retrieval  
12 analysis for more than a decade, and we have over  
13 100 more--triple digits plus--of metal-on-metal  
14 retrievals, what I would consider "runaway wear," I  
15 have not seen with metal-on-metal devices, and  
16 there is a lacking in definition of what that is.

17 The first issue is one that was curious to  
18 me as well in looking at the dataset. There were  
19 three femoral perforations in one of the  
20 metal-on-metal groups and none in the  
21 metal-on-polyethylene. That was interesting  
22 because that has nothing to do with the  
23 metal-on-metal bearing. And I thought, now, why  
24 does something like that happen, and I don't know  
25 the definite reason--it could be just bad luck in

1 those cases, that those are the only femoral  
2 perforations that those guys had ever had. But why  
3 would it happen in those cases?

4           How many of you guys are golfers? There  
5 is something called "the yips." Why does a golfer  
6 miss a 3-foot putt when he is putting for the  
7 match, but he doesn't miss the same putt when it is  
8 somewhere on the front 9, and nobody cares? It is  
9 because it is a different circumstance, and the  
10 mental process is different.

11           Perhaps could this be the same sort of  
12 thing where, when a guy is putting in the standard  
13 hip that he always puts in, the metal-plastic hip,  
14 it's just like business as usual, and he's not  
15 really thinking about it, and he executes his usual  
16 technique. But there is something different  
17 now--he is putting in one of the investigational  
18 devices, so the mental process and perhaps the  
19 physical execution might be different--an example  
20 of "the yips."

21           I don't know, but when I looked at that, I  
22 was trying to rationalize how that could happen,  
23 because putting in the femoral component which is a  
24 modular component and doesn't even have a bearing  
25 surface on it, why that would have a different

1 complication than in the metal-on-plastic.

2 I don't know if that--

3 DR. SKINNER: And how about the  
4 dislocation?

5 DR. SCHMALZRIED: There may be two  
6 elements to that. One might be something related  
7 to "the yips" and the intraoperative positioning  
8 and placement of the component. But one other  
9 issue that may play into this--and I need to be  
10 corrected if I am wrong on this--but it is my  
11 understanding that the depth of at least one of the  
12 metal-on-metal designs--it was not a full  
13 hemisphere. So in order to have larger range of  
14 motion prior to neck-socket impingement, the cup  
15 was intentionally a little bit shallow. That might  
16 change the intraoperative testing of stability and  
17 might encourage a surgeon to push the range of  
18 motion, have demonstrated instability, and change  
19 the position of the socket based on that.

20 Is that correct, Tom?

21 MR. CRAIG: This is Tom Craig, and I'm not  
22 even with the company that makes one of these  
23 things, so I can't answer that question, but I will  
24 ask one of the engineers to come forward.

25 MR. LANCASTER: I am Jim Lancaster, with

1 DePuy, in Product Development.

2 That is correct--one of the devices had  
3 less than 180 degrees of articular coverage.

4 DR. SKINNER: Thank you.

5 DR. YASZEMSKI: Thanks, Dr. Skinner.

6 We're going to finish up now and ask Dr.  
7 Li if he has any additional comments.

8 DR. LI: Yes, I have a question for Dr.  
9 Jacobs and one for Dr. Medley.

10 Josh, I think most of your work actually  
11 has been the basis for my concern for  
12 metal-on-metal debris. You have shown different  
13 reactivities versus polyethylene; you have shown  
14 increased serum levels in patients, different  
15 reactive pathways for metal over polyethylene.

16 So at the end of the day--and you have  
17 published in the past that this is an area of  
18 concern and should be followed--so where are we?  
19 Is your position still the same, or do you think  
20 there is enough information now where the concern  
21 is much less to you?

22 DR. JACOBS: It is a good question. What  
23 we are talking about is relative risks and  
24 benefits. The risks that we discuss relative to  
25 the biological effects of metal have not been

1 completely resolved and I think definitely need to  
2 be continually investigated, as we are certainly  
3 doing and many others.

4 But the benefits of this technology of  
5 reducing volumetric wear of an order of magnitude  
6 or more, and potentially reducing the complications  
7 of osteolysis with or without loosening, can also  
8 reduce risks to patients as well. There are with  
9 revision surgery definite risks, including a  
10 mortality rate that may be as much as three times  
11 that in primary total hips.

12 So I think the issue is that what we are  
13 trying to do is reduce the risks and morbidity  
14 associated with revision surgery, and in the  
15 process of doing that, we may engender some other  
16 risks, so there is this balance.

17 So is it still an area worth  
18 investigation? The answer is yes. I think we have  
19 enough information now to know what the potential  
20 risks may be and to begin to study them.

21 Can these risks that I am discussing be  
22 ascertained in a 2-year PMA? The answer is no.  
23 You'll get no additional information about these  
24 risks with a 2-year PMA.

25 And the other end of it is what special

1 controls can be imposed to get at potential  
2 20-25-year risks, and I don't see practical  
3 controls along those lines.

4           Therefore, I think down-classification is  
5 reasonable on that basis.

6           DR. LI: As a follow-up question, do you  
7 think for the size of debris--again, I provide you  
8 with credit for pointing this out to me in the  
9 past--that at issue might not be mass lost but  
10 definitely less metal lost in wear with  
11 polyethylene, but with the vast difference in size  
12 of particles, might essentially the biological  
13 burden/benefit not be nearly as great as the  
14 difference in mass lost?

15           DR. JACOBS: It's a great point, and the  
16 biological burden is different. What we don't know  
17 is what the bioreactivity is of nanometer-sized  
18 particles for the very reason that they are almost  
19 impossible to study, to isolate, to identify, the  
20 filter and then, in turn, to put them in our cell  
21 cultures. That is an area where, hopefully, we'll  
22 see some developments over the next 5 to 10 years.

23           But we don't have an idea of what the  
24 relative bioreactivity is of, say, a 10- or  
25 20-nanometer metal particle versus a 500-nanometer

1 metal particle. I just don't think it's known.  
2 Certainly there is a higher specific surface area  
3 with smaller debris, and that certainly could  
4 account for some of the elevations in serum and  
5 urine chromium cobalt that we have documented.

6           Some authors have suggested that in fact  
7 when you have debris that small, instead of having  
8 the cell undergo phagocytosis, which starts a whole  
9 intracellular machinery process to turn on a number  
10 of signalling cascades that can lead to the  
11 expression and secretion of proinflammatory  
12 cytokines, many of which can stimulate bone  
13 resorption, that the smaller particles will not  
14 actually initiate phagocytosis but instead will get  
15 into the cell via pinocytosis, which will bring up  
16 a host of different types of cellular responses.

17           So it is an area that is incompletely  
18 understood at the present time, and I don't think  
19 there are any clear answers.

20           DR. LI: Thank you.

21           DR. YASZEMSKI: Dr. Cheng?

22           DR. CHENG: Dr. Jacobs, I just want to  
23 follow the question on the same issue. I agree  
24 with you; I think from the standpoint of  
25 carcinogenicity, the numbers are required for so

1 many patients that you will never find out with  
2 some kind of study. So whether it is  
3 down-classified is not going to make a difference;  
4 you won't get the answer.

5           But one thing--when we look at induced  
6 sarcomas for various reasons, like a  
7 radiation-induced sarcoma, one of the issues is  
8 whether or not the tumor occurs at the site of  
9 injury in the case of radiation, or in this case,  
10 we might glean some evidence as to whether the  
11 tumor occurred, a sarcoma arose, at the site of the  
12 implant. It wasn't clear to me in the literature  
13 if it was at the site of the implant or just in any  
14 other site in the body.

15           DR. JACOBS: The study that is oft-quoted  
16 about the concern of lymphoma leukemias, the Visuri  
17 study, is also the same study that had a zero  
18 incidence of local sarcoma associated with the  
19 implant. So if you accept you, you'd have to  
20 accept the other.

21           Now, I have looked at this in the past,  
22 and in 1992, I surveyed the literature and found  
23 about two dozen case reports of malignancies  
24 associated with joint replacements. Since that  
25 time, maybe there have been another dozen. So we

1 are talking about in the world literature maybe 36  
2 to 40 cases of sarcomas associated with joint  
3 replacement devices; that is in the region. Now,  
4 granted these go unreported; probably all of us  
5 know of a few that are unreported. But still,  
6 considering the denominator is millions and  
7 millions of devices, and also pointing to the  
8 studies that have looked at local sarcomas, none of  
9 the studies has suggested an elevated rate of local  
10 sarcoma formation.

11 So the concern really isn't local sarcoma  
12 development; the concern is these remote  
13 hematopoietic malignancies.

14 DR. CHENG: I have the same opinion. My  
15 concerns that I mentioned in regard to the  
16 classification really deal with the other risks  
17 that might be answered by studies--the wear and so  
18 forth--and not the carcinogenicity.

19 DR. YASZEMSKI: Thank you.

20 DR. LI: I have one more question for Dr.  
21 Medley.

22 DR. YASZEMSKI: Dr. Li.

23 DR. LI: John, you have done as much  
24 metal-on-metal testing as anyone. You showed in  
25 one graph, for instance, the effect of clearance

1 and wear. As Dr. Schmalzried has pointed out many  
2 times, wear is multifactorial. The Petitioners  
3 have actually identified other parameters such as  
4 sphericity and surface roughness; they have talked  
5 about abduction angles, increased loading and  
6 activity levels.

7           This is perhaps an unfair question, but  
8 given all those multifactorials, if someone were to  
9 actually drop a load of support on you so that you  
10 could study these different variables, do you think  
11 there are some combinations in there that would in  
12 fact give you a much higher wear than you are  
13 currently measuring in what we have been calling  
14 kind of idealistic conditions?

15           DR. MEDLEY: That's a loaded question, but  
16 yes. What we are encouraged by is--we have tried a  
17 little bit of extreme testing. We have tried a bit  
18 of stop-start, other people have changed the  
19 kinematics, and we haven't seen anything too  
20 dramatically different than what we saw previously.  
21 In other words, the wear rates don't jump up.

22           Now, is there a combination of  
23 parameters--knowing clearance, knowing roughness,  
24 and knowing sphericity doesn't tell you everything  
25 about wear. In fact, wear in the general study in

ah

1 tribology is very poorly understood; even under  
2 much better controlled conditions, there are things  
3 that go on in wear tests that people don't  
4 understand.

5           So it is actually amazingly consistent  
6 data we are getting from this compared to what some  
7 of the other studies, like the wear of steels  
8 against each other.

9           So I think we knew something on the order  
10 of 50 percent of what is going on, and there is  
11 another 50 percent that we don't know, but our  
12 manipulation so far hasn't been able to produce  
13 anything dramatically different except if we allow  
14 the clearance to go very high, we do see an effect  
15 that is very strong, and if we allow the clearance  
16 to go very low or negative, we see a very strong  
17 effect there--at least a few people have seen it.

18           So it is an issue of having these  
19 parameters means that we have some control over the  
20 process, but we don't have a bottom line. We can't  
21 sit there and say, Give me an implant, I'll measure  
22 a few things, and I'll tell you what the wear is  
23 going to be, and I guarantee my result. We can't  
24 do that.

25           There is an ongoing scientific

1 consideration for wear testing. If suddenly there  
2 were completely unrestricted use in North America,  
3 that doesn't mean I would stop doing the testing,  
4 because I think there are still issues out there.  
5 But I think in the balance, the major problems we  
6 can spot, and I don't expect to see anything too  
7 dramatic happen as we look at strange combinations,  
8 or maybe even new geometries--dual-radius cups, new  
9 metal combinations that you have touched on--in  
10 other words, if you mixed a cast with a wrought,  
11 what would you see. I don't think you are going to  
12 see anything much worse; I don't think you are  
13 going to see anything that much better. You will  
14 see differences.

15           So my bottom line is that I think we are  
16 at the point now that we know enough about what is  
17 happening that we are reasonably confident that we  
18 can have low volumetric wear even under some of the  
19 more extreme conditions, but I don't say that we  
20 know everything about what is happening.

21           DR. LI: Thank you.

22           DR. YASZEMSKI: Thanks, Dr. Medley.

23           We're going to break for lunch now. I'd  
24 like to mention to the panel members that when we  
25 come back, and I'm going to go around the table and

1 ask each of them for their answers to and thoughts  
2 about Questions 1, 2, and 3, and then we'll ask Ms.  
3 Shulman to come up and help us fill out the  
4 worksheets.

5           It's 12:45 now; let's break until 1:45 and  
6 then reconvene with a round-robin discussion of the  
7 questions.

8           [Whereupon, at 12:45 p.m., the proceedings  
9 recessed to reconvene at 1:50 p.m. this same day.]

ah

## AFTERNOON SESSION

[1:50 p.m.]

1  
2  
3 DR. YASZEMSKI: The way we'll conduct the  
4 afternoon is we'll start by going around the table  
5 one time each for each of the three questions and  
6 ask each panel member their answer to and comments  
7 upon each question, and then we're going to use  
8 that information as a preliminary to working on the  
9 Device Classification Questionnaire.

10 As soon as we've got everybody seated,  
11 we'll get started with Question 1.

12 Could I ask you, please to put up Question  
13 1? We started last time with Dr. Finnegan, so I'm  
14 going to prompt Dr. Li that I'm going to start with  
15 you this time.

16 Could you read Question 1, please?

17 MR. STEIGMAN: Question 1. "Overall  
18 Risks. Has the Petitioner identified all the risks  
19 associated with this device type? If not, please  
20 identify any additional risks for metal-on-metal  
21 hips."

22 DR. YASZEMSKI: Dr. Li?

23 DR. LI: And the overall risks are in the  
24 box above in our handout; is that correct?

25 No, I have nothing to add to that list.

1 DR. YASZEMSKI: Okay. The list of overall  
2 risks, just for reference, is in the packet just  
3 above Question 1.

4 Dr. Skinner?

5 DR. SKINNER: I've got nothing to add.

6 DR. YASZEMSKI: Thank you.

7 Dr. Peimer?

8 DR. PEIMER: Nothing to add. Thank you.

9 DR. YASZEMSKI: Dr. Aboulafia?

10 DR. ABOULAFIA: Nothing to add.

11 DR. YASZEMSKI: Ms. Maher?

12 MS. MAHER: Nothing to add.

13 DR. YASZEMSKI: Dr. Larntz?

14 DR. LARNTZ: Nothing to add.

15 DR. YASZEMSKI: Dr. Cheng?

16 DR. CHENG: The only thing I thought of  
17 might be the ease of revision should that be  
18 necessary.

19 DR. YASZEMSKI: Thank you, Dr. Cheng.

20 Dr. Wright?

21 DR. WRIGHT: Yes, I think the Petitioner  
22 has identified all risks.

23 DR. YASZEMSKI: Dr. Lyons?

24 DR. LYONS: I agree.

25 DR. YASZEMSKI: Dr. Finnegan?

1 DR. FINNEGAN: I actually think  
2 carcinogenicity should be added to the list.

3 DR. YASZEMSKI: So in answer to Question  
4 1, it is the general feeling of the panel that  
5 Petitioner has identified all the risks, with the  
6 addition perhaps of commenting on ease of revision  
7 and carcinogenicity.

8 May I ask the FDA if we have adequately  
9 discussed and answered this question to your  
10 satisfaction.

11 DR. WITTEN: Yes. Thanks.

12 DR. YASZEMSKI: Thank you.

13 We're going to move on now to Question 2.  
14 Could I ask that you please put up Question 2?

15 MR. STEIGMAN: Question 2. "Based on the  
16 risks of migration and loosening of metal-on-metal  
17 hip implants, has the petition adequately  
18 identified special controls to minimize these  
19 risks? If not, please identify additional special  
20 controls that can be used to minimize these risks."

21 DR. YASZEMSKI: Thank you.

22 Dr. Li?

23 DR. LI: I guess, given that I don't think  
24 from the information I saw that migration and  
25 loosening are actually problems in the 2-year

1 follow-up, I guess I would have to answer that  
2 there are no additional special controls.

3 DR. YASZEMSKI: Thank you.

4 Dr. Skinner?

5 DR. SKINNER: I've got nothing to add to  
6 that.

7 DR. YASZEMSKI: Thank you.

8 Dr. Peimer?

9 DR. PEIMER: As a biomechanical babe in  
10 the woods, I need to ask if this is the place where  
11 one would comment on effective radius limitations,  
12 if I'm saying it correctly, because that would  
13 impact on loosening, although I agree that in the  
14 2-year category, migration and loosening are not  
15 significant risks; I am concerned about longer term  
16 and with reference to the historical devices.

17 DR. YASZEMSKI: Thank you.

18 Dr. Aboulafia?

19 DR. ABOULAFIA: First, specifically in  
20 answer to the question, I would say yes, they have,  
21 but I'm not sure if they have identified what the  
22 risks of migration and loosening are, based on  
23 limited data at 2-year follow-up.

24 DR. YASZEMSKI: Thank you.

25 MS. MAHER: I would say yes, they have

1 addressed these, and I would also add that the  
2 2-year follow-up is what most PMAs are also  
3 approved on to go forward, and we are not talking  
4 about approval of a specific device; we are talking  
5 about the down-classification to Class II, so a  
6 different route to go through a marketing  
7 application review.

8 DR. YASZEMSKI: Thank you.

9 Mr. Dacey?

10 MR. DACEY: No comments.

11 DR. YASZEMSKI: Dr. Aboulafia?

12 DR. ABOULAFIA: I was going to say I  
13 understand 2-year follow-up; I'm saying there is  
14 not good 2-year follow-up.

15 DR. YASZEMSKI: Thank you.

16 Dr. Larntz?

17 DR. LARNTZ: No additional comments.

18 DR. YASZEMSKI: Thank you, Dr. Larntz.

19 Dr. Cheng?

20 DR. CHENG: The only comment I have is  
21 that I don't think these risks can be really  
22 assessed at 2 years, or defined; the problems are  
23 going to be longer-term.

24 DR. YASZEMSKI: Thank you, Dr. Cheng.

25 Dr. Wright?

1 DR. WRIGHT: Yes, I think they have  
2 addressed the issue.

3 DR. YASZEMSKI: Thanks, Dr. Wright.  
4 Dr. Lyons?

5 DR. LYONS: Yes, I think for Question 2,  
6 that's fine.

7 DR. YASZEMSKI: Thanks, Dr. Lyons.  
8 Dr. Finnegan?

9 DR. FINNEGAN: I'm really going to get  
10 myself a reputation here. Actually, I think part  
11 of the concern comes from the fact that they tried  
12 to include too many available prostheses on the  
13 market or potential available prostheses on the  
14 market, and if they limited the prostheses that  
15 they were putting into this group, i.e., without  
16 threads and perhaps without the poly link, that  
17 this would be less of a concern.

18 DR. YASZEMSKI: Thank you, Dr. Finnegan.

19 May I ask you to put up the third question  
20 now, and while he is doing that, may I ask Dr.  
21 Witten--have we adequately discussed Question 2 for  
22 the FDA?

23 DR. WITTEN: Yes.

24 DR. YASZEMSKI: Thank you, Dr. Witten.

25 MR. STEIGMAN: Question 3. "Does the wear

1 testing proposal, including the use of a negative  
2 control--that is, a 28-mm legally marketed  
3 metal-on-metal hip having design parameters within  
4 a specified range--adequately minimize the  
5 identified risks? Is a positive control such as  
6 early devices needed for comparison as well? If  
7 not, will the proposed wear testing minimize the  
8 risks associated with wear?"

9 DR. YASZEMSKI: Dr. Li?

10 DR. LI: I do not believe the wear testing  
11 protocol, including the negative control,  
12 adequately minimizes the identified risks. Do you  
13 just want a yes or no at this point in time?

14 DR. YASZEMSKI: I'd like to hear what you  
15 might think we should add to make it appropriate.

16 DR. LI: Okay. I am concerned--with no  
17 disrespect to Dr. Medley and other people who have  
18 done metal-on-metal hip simulators--that the number  
19 of factors that have been actually directly studied  
20 is relatively small; we really don't know what the  
21 interactions are between the parameters provided by  
22 the applicant and also parameters not provided by  
23 the applicant, including things like increased  
24 loading, increased activity levels, high abduction  
25 angles, and things like that, or different designs,

1 if they are going to include the polyethylene  
2 sandwich type of construct. I don't believe the  
3 simple, if you will, testing provided will  
4 adequately answer those questions.

5 DR. YASZEMSKI: May I ask also, Dr. Li, to  
6 have you comment on the need for a positive  
7 control?

8 DR. LI: Yes. I believe a positive  
9 control is necessary. The suggestion here would be  
10 to test an earlier device; I'm not sure that is  
11 particularly meaningful. But for instance, a  
12 positive control could be providing testing the  
13 range of their design parameters. In other words,  
14 if you go outside their roughness range or outside  
15 their sphericity range, would in fact the wear rate  
16 go up?

17 So I think you need some way to generate a  
18 bad result. Otherwise, you have the very unreal  
19 expectation that no matter what you do, the device  
20 is perfect--but I have never really run across a  
21 device like that.

22 DR. YASZEMSKI: Thank you, Dr. Li.

23 Dr. Skinner?

24 DR. SKINNER: I hesitate to disagree with  
25 my esteemed colleague. It is my feeling that

1 unless we know what the failure mechanism is likely  
2 to be in the positive control, I don't know what we  
3 are going to gain from putting in a control that  
4 doesn't necessarily coincide with that failure  
5 mechanism. We're going to know that it wears more,  
6 but I'm not sure what information we would get out  
7 of that.

8           You've got a negative control; it either  
9 wears as much as the negative control, or it  
10 doesn't wear as much as the negative control.  
11 Adding a positive control that you know is going to  
12 wear more doesn't, as far as I see, do anything but  
13 raise the cost.

14           So I would disagree.

15           DR. YASZEMSKI: May I ask Dr. Skinner,  
16 then, as the question is posed, if you don't feel  
17 that we need a positive control, is the wear  
18 testing system as proposed adequate in your  
19 perspective?

20           DR. SKINNER: If I were allowed to vote, I  
21 would say yes.

22           DR. YASZEMSKI: Okay. Thank you.

23           Dr. Peimer?

24           DR. PEIMER: I don't--I would agree that  
25 there is not a need for a positive control, but I

1 would also agree that the design parameters of the  
2 wear testing protocol don't adequately evaluate  
3 failure. One needs to find out how a device fails,  
4 and in adding a positive control, we know many of  
5 the reasons why that device fails, but we need to  
6 find out why this device would fail, as surely it  
7 will in some people, and then design around that.  
8 And that issue is not addressed. Whether that is  
9 found in a mechanical model or in an animal, an in  
10 vivo simulation, has to be specifically addressed  
11 in each prosthesis.

12 So I realize it is a conflicted answer,  
13 but I don't think we need a positive here; however,  
14 the current construct of the negative control is  
15 not adequate to derive the negative data that you  
16 really need before it is inflicted on patients.

17 DR. YASZEMSKI: May I ask if you have a  
18 particular set of tests or test that would make it  
19 appropriate?

20 DR. PEIMER: I might be in Stockholm if I  
21 did.

22 I would like to see the angular loading  
23 changed. I would like to see different bearing  
24 forces applied at different points in a test cycle  
25 so that one could at least, if one is going to use

1 the word "simulation," for better or for worse, at  
2 least simulate what happens when a person  
3 stretches, falls, twists, and hits the joint  
4 surfaces at different angles and with different  
5 forces.

6 So I guess I don't have a better answer  
7 than that.

8 DR. YASZEMSKI: Thank you.

9 Dr. Aboulafia?

10 DR. ABOULAFIA: I actually don't think Dr.  
11 Peimer's answer is conflicting. I agree with him.  
12 I don't think you need positive controls, and I do  
13 think that the proposed wear testing is not  
14 sufficient to minimize the risks related to wear  
15 for the reasons that have been specified by Dr. Li  
16 and Dr. Peimer, and I agree; I think just simple,  
17 non-ideal testing should be done.

18 DR. YASZEMSKI: Thank you.

19 Before we come around, I want to come back  
20 to Dr. Li.

21 Dr. Li?

22 DR. LI: I'd like to add one thing--I'm  
23 sorry. I guess one of the reasons why I believe  
24 the current testing protocol is inadequate is  
25 because it is basically based on a volumetric or a

1 weight loss type of measurement for wear, the idea  
2 being that if you are the same or less than  
3 polyethylene in the measurement, you'll be better  
4 off, but if the particles are 10 or 100 times  
5 smaller, the surface area change is significantly  
6 smaller--in fact, if you are 100 times smaller in  
7 wear size, the biological burden may in fact be no  
8 different even though the magnitude of the wear you  
9 are measuring is substantially less.

10 DR. YASZEMSKI: Thank you, Dr. Li.

11 Ms. Maher?

12 MS. MAHER: I actually don't see the need  
13 for a positive control, especially using the early  
14 devices, given that you are not going to find  
15 anybody willing to make a sivage [phonetic] just to  
16 test against.

17 I do think that they have a good beginning  
18 of where they needed to be for the wear testing.  
19 Maybe it needs to have some tweaks made on it, but  
20 I think they have made a very good start.

21 DR. YASZEMSKI: Thank you.

22 Mr. Dacey?

23 MR. DACEY: Nothing.

24 DR. YASZEMSKI: Thank you.

25 Dr. Larntz?

1 DR. LARNTZ: I guess my only concern is  
2 that when they identify the various parameters that  
3 they need to change due to wear testing, they do it  
4 over a wide enough range and in a factorial fashion  
5 where they try all combinations or at least some  
6 fractional factorial combination of factors to make  
7 sure they identify the effects. So just to make  
8 sure they do a well-designed study to make sure  
9 they understand the effects where the parameters  
10 are changing.

11 DR. YASZEMSKI: Thank you, Dr. Larntz.  
12 Dr. Cheng?

13 DR. CHENG: I'm a little concerned that we  
14 are just focusing on wear as the main risk here.  
15 It is the difference in the bearing surface that we  
16 are testing, but it is really the biological  
17 consequence of the wear that we are concerned  
18 about, with wear being directly related to that, of  
19 course.

20 So I don't think it can completely  
21 identify the risks. Part of this is driving, I  
22 suppose, at what Dr. Li has said about the  
23 different particles, the body will handle them  
24 differently.

25 My only other comment is that I think all

1 sizes within the range specified in the proposal  
2 should be tested, and I don't think you need a  
3 positive control.

4 DR. YASZEMSKI: Thank you, Dr. Cheng.  
5 Dr. Wright?

6 DR. WRIGHT: I do not think that the  
7 testing proposal adequately minimizes the risk, and  
8 I agree with Dr. Cheng in that I think that the  
9 petition is so broadly worded and wide-open, and I  
10 think I would really be more in favor of testing  
11 what the implants are rather than getting some big  
12 variables. I don't think we need a positive or a  
13 historical control, but I do not think the testing  
14 parameters are adequate for the identified risks.

15 DR. YASZEMSKI: And what would you add,  
16 specifically?

17 DR. WRIGHT: Well, the petition, as I  
18 understand it, doesn't have any limitation on size  
19 of components, and I think that specifically, the  
20 implant sizes need to be specified and tested,  
21 because I think there is probably a difference in  
22 the testing patterns of different sizes.

23 DR. YASZEMSKI: Thank you, Dr. Wright.  
24 Dr. Lyons?

25 DR. LYONS: I had a comment on this

1 question. I think it actually leads back to  
2 Question 2, but it can be answered just through  
3 Question 3, on the wear. I have some concerns  
4 about the wear and the sandwich design and a couple  
5 other things.

6 I wonder if I could ask Tom Schmalzried  
7 for a point of clarification?

8 DR. YASZEMSKI: Please go ahead.

9 DR. LYONS: Could you just go over the  
10 presentation to the effect that the testing they  
11 feel from the manufacturing side is sufficient to  
12 address the sandwich issue or the impingement  
13 components and try to expand a little bit more for  
14 me, because I wasn't real clear about the proposal.  
15 I thought everything was being presented for  
16 declassification, yet the data that I studied, the  
17 stacks in my little notebook here, really didn't  
18 tell me a lot about creep and other issues that I  
19 was concerned about.

20 DR. SCHMALZRIED: I'm going to try to  
21 address that issue. What I think John is basically  
22 getting at is the complexities of wear simulator  
23 testing and how you draw a relationship or make a  
24 relationship to what happens clinically.

25 The variability that occurs clinically is

1 tremendous. I'll pick one that our group happens  
2 to have studied, and that is patient activity. We  
3 documented a 45-fold range in patient activity,  
4 meaning that you've got some patients who don't do  
5 much and other patients who do a tremendous amount.  
6 So when you talk about a million cycles as the  
7 equivalent of a year in vivo, the answer is, well,  
8 who is that, because the patients that we're  
9 talking about who are the targets for these  
10 alternate bearings are people who are multiples of  
11 that.

12           So that's just one. Now, I don't take the  
13 same step every time. The steps I take aren't the  
14 same as yours. So there is certainly variability  
15 in the cycling. How do we most efficaciously  
16 address that in a simulator test?

17           The problem that we have is a paucity of  
18 clinical information to guide us as to what  
19 modifications to make in the wear simulator  
20 protocols.

21           It wasn't suggested by the panel, but I  
22 think I'd like to get on the record that recent  
23 information indicates that stop-start cycling is  
24 something that needs to be looked at, and inducing  
25 some separation between the bearings during the

1 loading cycle should be looked at because we've got  
2 some clinical evidence that these things may be  
3 important.

4           The position factor--we have to remember  
5 that all of these things that we are talking about  
6 are not exclusive to metal-on-metal. We are  
7 talking about surgeons putting in device and the  
8 variability that affects polyethylene and the wear  
9 of polyethylene. And the creep issue I'll come  
10 back to in just a minute. The position sensitivity  
11 issue we have to be very careful about the  
12 "compared to what?" One piece of information that  
13 might be helpful for the panel to know, clinically,  
14 there is evidence--our group reported in the  
15 Journal of Arthroplasty a couple of years ago about  
16 long-term McKee-Farrar survivors. These are  
17 patients who in the seventies had a  
18 first-generation metal-on-metal device in that  
19 survived more than 20 years.

20           One of the factors that was actually  
21 associated with a better chance of long-term  
22 survival was the high lateral opening and a big  
23 abduction angle. You might ask, gee, why is that.  
24 Well, it is not a bearing surface issue; it is an  
25 arc of motion issue. The McKee-Farrar because it

1 had a broad neck on the femoral component was more  
2 likely to have neck socket impingement at a lower  
3 range of motion. By having a high abduction angle,  
4 it meant there was greater excursion before you  
5 could get neck socket impingement, and that was  
6 actually associated with a better clinical  
7 survival.

8 So we have to be careful about the way we  
9 design these things because we are not really just  
10 talking about a bearing; we are talking about a  
11 device that is ultimately in a patient, and there  
12 is relatively positioning that is outside the  
13 control of what we can monitor here.

14 The creep issue is one--if we are  
15 concerned about that, let me throw one out to you.  
16 When you have a metal-on-plastic hip that everybody  
17 is using--the standard right now--they creep; the  
18 center of rotation of the femoral head moves into  
19 the center of rotation of the cup, and with time,  
20 there is wear so it moves in further. Creep is  
21 something that basically has its greatest effect in  
22 the first year to 18 months.

23 We see late dislocations of  
24 metal-on-plastic hips. There is an initial rise,  
25 and then it is down, and then, out past 5 years, it

1 comes up again. One of the contributing factors is  
2 that you have impingement sooner because as the  
3 head becomes relatively captured by the socket, it  
4 impinges sooner.

5 So in all fairness, if we are going to  
6 talk about creep as an issue that might affect the  
7 long-term performance, that is an issue that is of  
8 greater concern to me for metal-on-plastic hips.

9 I think that the computer modeling can  
10 adequately address the effect of creep in the metal  
11 sandwich because a lot is known about the rate of  
12 creep for the given polymers that are used, and a  
13 model can easily be made to show what the pure  
14 effect of creep would be on the center of rotation,  
15 and you can model the range of motion and  
16 likelihood for impingement from that. I think that  
17 lends itself very nicely to a computer model.

18 If that's okay, we could--

19 DR. YASZEMSKI: Dr. Lyons, has that  
20 adequately answered your concern?

21 DR. LYONS: Yes. I think what it does is  
22 tell me that I think the train of thought is that  
23 we should have some more wear testing to answer  
24 Question 3, and there may be more parameters than  
25 we can maybe nail down right this minute, but

1 several of them. I defer to Dr. Li on some of  
2 these, and actually, the presenters know some of  
3 these potential problems.

4 DR. SCHMALZRIED: The one closing comment  
5 that I would like to make is that we don't know  
6 what the significance is clinically. Dr. Medley  
7 showed a bunch of graphs--this one wears this much  
8 and that one wears that much. The problem is that  
9 we don't know what that means. If it were as  
10 simple as approving a bearing, you would obviously  
11 just say "We want the one that demonstrates the  
12 lowest wear in whatever test." But you have to ask  
13 how do we know if that really represents what goes  
14 on clinically.

15 So I urge caution to the panel about  
16 requesting more wear simulator testing when I am  
17 suggesting that we don't really understand what  
18 tests are going to be important in the clinical  
19 situation. There just isn't enough clinical  
20 understanding to know--where testing can be done,  
21 but how do we interpret the information. That's  
22 the thing that's on my mind.

23 DR. YASZEMSKI: Thanks very much, Dr.  
24 Schmalzried.

25 Dr. Finnegan, comments?

1 DR. FINNEGAN: Nothing to add.

2 DR. YASZEMSKI: Dr. Witten, have we had  
3 adequate discussion from the FDA's perspective on  
4 Question 3?

5 DR. WITTEN: Well, it's still not clear to  
6 me from your answer--at least I understand that  
7 some of the answers were yes and some were no to  
8 the last part of the question--"will the proposed  
9 wear testing minimize the risks associated with  
10 wear?" So, some people answered yes, and some no.  
11 I guess what we would like to hear is is there  
12 testing that you all can describe that will  
13 minimize the risks associated with wear.

14 DR. YASZEMSKI: To summarize what I  
15 thought I understood from the discussion, it was  
16 that a majority of the panel thought that a  
17 positive control was not necessary, and a majority  
18 thought that some additional wear testing was  
19 necessary. Examples of those additions would  
20 include changes in the angular loading, changes  
21 including different bearing forces applied, and  
22 testing of the actual sizes that are included in  
23 the petition.

24 If I could come back, Dr. Li, since you  
25 are our expert on this, can you concisely describe

1 for FDA those additions that we think would make  
2 the wear testing--minimize the risks?

3 DR. LI: Yes. I would add to it the two  
4 that Dr. Schmalzried just pointed out--essentially,  
5 the pulling apart of the femur from acetabulum that  
6 Doug Dennis has shown in fluoroscopy.

7 What was the other one, Tom?

8 DR. SCHMALZRIED: Stop-start.

9 DR. LI: Start-stop. So I agree those are  
10 two important parameters. And although most of the  
11 group thought that a positive control wasn't  
12 necessary, in my view, for instance, testing the  
13 range of the design parameters the applicant put  
14 out could represent essentially a positive control.  
15 For instance, if they say one of the measurements  
16 has to be greater than 30 and less than 200, one  
17 would hope, then, if that parameter range had any  
18 sense to it that if you went outside that range,  
19 the wear would be high.

20 Now, it's true that we don't know what the  
21 clinical result is, but although if you get a good  
22 result in a simulator, you may not get a good  
23 clinical result, I have yet to see a bad clinical  
24 simulator result turn into a good clinical result.

25 So if you get outside, for instance, the

1 sphericity range or the clearance range, and you  
2 get a high wear result, I would actually call that  
3 a positive control. I agree with the other people  
4 that making old devices--there's nothing in it for  
5 that--but I think that if you are going to put  
6 specifications for parameters, you actually have to  
7 have some data that backs up those parameters  
8 rather than just trying to collect a range that  
9 represents commercially existing devices.

10 DR. YASZEMSKI: Thank you, Dr. Li.

11 Dr. Witten, is this extra discussion  
12 adequate, or shall we go further--Dr. Cheng?

13 DR. CHENG: Mike, I didn't hear you  
14 mention my comment regarding the biologic  
15 consequence--I think this was touched upon by Dr.  
16 Schmalzried as well. Maybe we can find out whether  
17 or not a metal-on-metal bearing sheds more metal in  
18 wear or not, but it is really the consequence of  
19 that that we want to know. Sometimes we don't know  
20 how to test for that. I wish I had more background  
21 to tell you what biologic tests to do to look  
22 for--maybe you've got inject the metal particles  
23 into an animal for a while to see if it develops  
24 renal failure or something. If, 30 years ago, we  
25 had run wear simulator tests on polyethylene, and

1 one had a little bit more wear and one had a little  
2 bit less wear, I'm not sure anybody would have  
3 known that that would have caused osteolysis. Back  
4 then, people thought this was due to cement.

5 So here we are in 2001 looking at metal  
6 debris, and maybe we get a component which  
7 generates less metal debris, but we may have some  
8 other problems to deal with later, and I can't  
9 predict what that will be, but I'm sure it's a real  
10 possibility.

11 DR. YASZEMSKI: Thank you, Dr. Cheng.

12 I am also hesitating. I had that on the  
13 list, and I was trying to make a list of those  
14 things for which we could make a specific  
15 recommendation regarding a type of test, and as you  
16 mentioned in your comment, I am also not certain  
17 that I could recommend a particular type of test to  
18 assess the biologic consequences of wear.

19 But with that uncertainty in mind, shall  
20 we have further discussion, Dr. Witten, or will  
21 this serve FDA's purposes in answering Question 3?

22 DR. WITTEN: That will serve our purposes  
23 unless anyone else has a comment related to what  
24 Dr. Cheng just mentioned.

25 DR. YASZEMSKI: Are there other comments

1 on ways to possibly assess the biologic  
2 consequences of wear?

3 Dr. Peimer?

4 DR. PEIMER: I realize that this may be  
5 begging the obvious, but if we know that wear  
6 debris is an issue, and we know that there are a)  
7 systemic effects, we create a systemic model, or  
8 one creates systemic model; and b) local  
9 effects--and we also understand that microparticle  
10 size as well as dosing affects the substrate cell  
11 response--that would be another test that would be  
12 applied.

13 If we were to grind up--and now we know  
14 that if we grind up certain things even though they  
15 are not cytotoxic, they induce the inflammatory  
16 cascade that was mentioned earlier and osteolysis.  
17 Some of these may not, but we ought to know that.

18 So since we are looking at wear generation  
19 and are not sure where that's going to go--no pun  
20 intended--but we are not sure where that's going to  
21 go, at least test the obvious, those systemic  
22 effects of the microparticles and local effects in  
23 the synovial tissues, muscle and in bone--on bone  
24 and in bone.

25 DR. YASZEMSKI: Thank you.

1           If we can, I'd like to ask Ms. Marjorie  
2 Shulman to come up with the classification  
3 worksheets and help us apply the answers to  
4 Questions 1, 2, and 3 that we just discussed toward  
5 filling out the worksheets.

6           I'd like to thank Dr. Skinner for his  
7 contributions to the discussion, and we'll recuse  
8 him from the remainder of the meeting today.

9           For purposes of the record, I'm going to  
10 make the suggestion--and I'll ask from commentary  
11 from the panel members or FDA, and if someone would  
12 like to lodge a comment or disagreement--that there  
13 are two classifications proposed--the hip joint  
14 metal-on-metal semi-constrained with the cemented  
15 acetabular component and prosthesis; and hip joint  
16 metal-on-metal semi-constrained with porous coated  
17 uncemented acetabular prosthesis.

18           I am going to suggest that we fill out the  
19 worksheet for both of them at once rather than go  
20 through the worksheets twice, since the differences  
21 between them are not differences in the bearing  
22 surface.

23           Is there any objection to that?

24           [No response.]

25           DR. YASZEMSKI: Hearing none, we'll

1 proceed with the worksheets that Ms. Shulman is  
2 handing out.

3 I'd like to mention wit the panel members  
4 that the way we'll proceed as we discuss the  
5 entries in the reclassification worksheet and the  
6 supplemental data sheet is that I'd like each panel  
7 member to fill out his or her own sheet and then,  
8 as we reach a consensus, I'll pool your answers  
9 into one that I'll fill out here which I will read  
10 at the end, and the one that I read from will be  
11 the one we vote one.

12 MR. DEMIAN: Margie, just to note for the  
13 record, this form is still valid--is that  
14 correct--because it has an expiration date on it--I  
15 don't know if it is like polyethylene--but it says  
16 "January 2000." I still think it's good, isn't it?

17 MS. SHULMAN: Yes, the form is still good.  
18 It is not helpful, but it's good.

19 MR. DEMIAN: Okay.

20 DR. YASZEMSKI: Marjorie, go ahead.

21 MS. SHULMAN: We'll start with question 1.

22 "Is the device life-sustaining or  
23 life-supporting?"

24 I don't know how you want to start.

25 DR. YASZEMSKI: We can just go around and

1 ask each person to answer individually.

2 Dr. Aboulafia?

3 DR. ABOULAFIA: I would say yes in the  
4 sense that it improves quality of life.

5 DR. YASZEMSKI: Okay.

6 Dr. Peimer?

7 DR. PEIMER: Yes, it's life-supporting;  
8 quality of life.

9 DR. YASZEMSKI: Dr. Li?

10 DR. LI: Yes.

11 DR. YASZEMSKI: Dr. Finnegan?

12 DR. FINNEGAN: I guess--I was going to say  
13 no, but--

14 DR. YASZEMSKI: Feel free to say no.

15 DR. FINNEGAN: No.

16 DR. YASZEMSKI: Dr. Lyons?

17 DR. LYONS: I'd say no, it's not  
18 life-sustaining. It is supporting to a degree, but  
19 I'd say no generally.

20 DR. YASZEMSKI: Dr. Wright?

21 DR. WRIGHT: No.

22 DR. YASZEMSKI: Dr. Cheng?

23 DR. CHENG: I don't think this supports  
24 life.

25 DR. YASZEMSKI: Dr. Larntz?

1 DR. LARNTZ: Yes.

2 DR. YASZEMSKI: Thank you.

3 MS. SHULMAN: So on the first one, the  
4 majority is yes; correct?

5 DR. YASZEMSKI: I thought it was split  
6 pretty even.

7 MS. SHULMAN: Okay, it's split.

8 DR. PEIMER: Is there someone here from  
9 Florida?

10 [Laughter.]

11 DR. YASZEMSKI: Dr. Aboulafia?

12 DR. ABOULAFIA: Can FDA give us an example  
13 of things that are considered life-supporting?  
14 Does it need to be a cardiac pacemaker that, without  
15 it, you'd die; or does it have to be something that  
16 promotes the quality of life?

17 MS. SHULMAN: Hold on one second.

18 DR. YASZEMSKI: In the event of a 4-4 tie,  
19 which I think this is, I'll cast a vote, and I am  
20 going to vote no.

21 DR. WITTEN: I think that usually that  
22 category is for things that are literally  
23 life-sustaining or life-supporting. And I think  
24 what Dr. Aboulafia is mentioning about improving  
25 quality of life is--well, you're going to get to

1 Item 2, so you'll get to answer that question.

2 DR. YASZEMSKI: So we'll check "No" for  
3 Answer 1.

4 Number 2.

5 MS. SHULMAN: Number 2. "Is the device  
6 for a use which is of substantial importance in  
7 preventing impairment of human health?"

8 DR. YASZEMSKI: Dr. Aboulafia?

9 DR. ABOULAFIA: I'll take yes on that one.

10 DR. YASZEMSKI: Dr. Peimer?

11 DR. PEIMER: Yes again.

12 DR. YASZEMSKI: Dr. Li?

13 DR. LI: Yes.

14 DR. YASZEMSKI: Dr. Finnegan?

15 DR. FINNEGAN: Yes.

16 DR. YASZEMSKI: Dr. Lyons?

17 DR. LYONS: Yes.

18 DR. YASZEMSKI: Dr. Wright?

19 DR. WRIGHT: Yes.

20 DR. YASZEMSKI: Dr. Cheng?

21 DR. CHENG: Yes.

22 DR. YASZEMSKI: Dr. Larntz?

23 DR. LARNTZ: Yes.

24 DR. YASZEMSKI: I think we have a  
25 unanimous "Yes" for Number 2.

1 Number 3.

2 MS. SHULMAN: Number 3. "Does the device  
3 present a potential unreasonable risk of illness or  
4 injury?"

5 DR. YASZEMSKI: Dr. Aboulafia?

6 DR. ABOULAFIA: It's going to be tough. I  
7 want to say no, but I think there is not sufficient  
8 data to answer the question.

9 DR. YASZEMSKI: Your answer, then, for the  
10 purposes of the sheet? I'm going to put you on the  
11 spot and ask you for a yes or a no.

12 DR. ABOULAFIA: Yes.

13 DR. YASZEMSKI: Thank you.

14 Dr. Peimer?

15 DR. PEIMER: No.

16 DR. YASZEMSKI: Dr. Li?

17 DR. LI: So if you are uncertain that  
18 there is enough information, the answer would be  
19 "yes"? Is that what I'm getting?

20 DR. YASZEMSKI: I think you have to  
21 balance the strengths and weaknesses and choose  
22 "yes" or "no."

23 DR. LI: Another one of those adult  
24 decisions.

25 I guess I'll say yes to stay consistent

1 with later answers.

2 DR. YASZEMSKI: Thank you.

3 Dr. Finnegan?

4 DR. FINNEGAN: No.

5 DR. YASZEMSKI: Dr. Lyons?

6 DR. LYONS: No.

7 DR. YASZEMSKI: Dr. Wright?

8 DR. WRIGHT: No.

9 DR. YASZEMSKI: Dr. Cheng?

10 DR. CHENG: Yes.

11 DR. YASZEMSKI: Dr. Larntz?

12 DR. LARNTZ: No.

13 DR. YASZEMSKI: The noes are in the  
14 majority, and we are going to answer "No" to that  
15 one.

16 MS. SHULMAN: Let me clarify something.  
17 The definition of "life-supporting" or  
18 "life-sustaining" from 21 CFR 860.3: "A  
19 life-supporting or life-sustaining device means a  
20 device that is essential to or that yields  
21 information that is essential to the restoration or  
22 continuation of a bodily function important to the  
23 continuation of human life."

24 DR. FINNEGAN: Did lawyers write that?

25 [Laughter.]

1 DR. YASZEMSKI: Thank you, Ms. Shulman.

2 We're going to move on to Number 4, which  
3 is "Did you answer 'yes' to any of the above three  
4 questions?"

5 So Number 4 is "yes."

6 Having answered "yes" to Number 4, we go  
7 directly to Number 7.

8 Ms. Shulman.

9 MS. SHULMAN: "Is there sufficient  
10 information to establish special controls to  
11 provide reasonable assurance of the safety and  
12 effectiveness?"

13 DR. YASZEMSKI: Before we answer this, I  
14 might ask if we could ask Mr. McGunagle to come up,  
15 because some of these controls, performance  
16 standards, post-market surveillance, et cetera,  
17 have specific definitions associated with them, and  
18 I think we should all have them fresh in our minds  
19 before we proceed.

20 If I can, Mr. McGunagle, ask you to make a  
21 presentation on that.

22 DR. WITTEN: Not performance standards;  
23 he's going to talk about the other types of  
24 post-market controls.

25 DR. YASZEMSKI: Post-market. Thank you,

1 Dr. Witten.

2 DR. MCGUNAGLE: Unfortunately, I have lost  
3 the use of the projector screen, but that's not a  
4 problem as long as you don't mind working without  
5 pictures.

6 DR. YASZEMSKI: Can we get it back up?

7 DR. WITTEN: Maybe we should introduce Dr.  
8 McGunagle, too, since not everybody knows you.

9 Dr. MCGUNAGLE: Yes. I am Daniel  
10 McGunagle. I work for the FDA's Office of  
11 Surveillance and Biometrics. We handle a lot of  
12 the monitoring of what's going on, and we receive  
13 your MDRs, review your MDRs, analyze them, and we  
14 take advantage of whatever information sources we  
15 can find--although I can't seem to get into this  
16 one.

17 DR. WITTEN: So that's the office that  
18 looks at the post-market types of data like MDRs  
19 and some of the other topics, like tracking, that  
20 sometimes come up in these discussions.

21 [Slide.]

22 DR. MCGUNAGLE: As you can see on the  
23 screen, our major post-market evaluation tools are  
24 Adverse Event Reporting Systems--this includes MDR,  
25 specific investigations of reported outbreaks,

1 regulatory inspections, laboratory-based  
2 investigations, use monitoring, and registries, but  
3 the registries are by and large registries that  
4 other people are preparing and operating, and the  
5 owners have granted us access, either as part of  
6 some kind of agreement or because they would like  
7 to have our analysis.

8           The second item in our evaluation tools is  
9 Section 522 studies.

10           [Slide.]

11           Our Adverse Event Reporting is a passive  
12 listening-type system. Parties such as  
13 manufacturers and user facilities have requirements  
14 to report, and they report to us on an annual  
15 basis. The reports that they receive are primarily  
16 voluntary reports, so we are all dependent on how  
17 honest and forthright everybody would like to be.

18           [Slide.]

19           This is a list of the items that  
20 manufacturers are required to report to us and the  
21 time frames in which they must react. And the last  
22 item down there is an approximate--that 80,000 is  
23 now 2 years old, and the numbers are dwindling over  
24 time.

25           [Slide.]

1           So what happens to reports--these are what  
2 are commonly called MDR reports. They are reviewed  
3 from a variety of perspectives. We have analysts  
4 who have background and training in various medical  
5 areas, and they review the reports, look for  
6 patterns, look for the appearance of new failures  
7 modes, new problems, et cetera.

8           [Slide.]

9           Follow-up actions taken as a result of  
10 what we see in MDR are presented here. We ask for  
11 information. We initiate investigations and  
12 involve the rest of the Center and sometimes  
13 manufactures when they are willing to participate.  
14 We initiate inspections of firms and initiate  
15 regulatory or deliberative action.

16           522 studies are what everyone refers to as  
17 "post-market surveillance studies." The law was  
18 amended in 1997, and the current presentation--I'll  
19 spare you the legalese--this is the part that is  
20 relevant--"FDA may require 522 for Class II or  
21 Class III devices the failure of which is  
22 reasonably likely to have serious adverse health  
23 consequences or is implanted for greater than one  
24 year or is a  
25 life-supporting/life-sustaining"--Marjorie, can I

1 have that definition again, please--"used outside  
2 of the user facility."

3 [Slide.]

4 Now, 522 also has some very serious  
5 limitations in that the manufacturer submits a plan  
6 in response to a post-market surveillance order;  
7 FDA reviews the plan within 60 days to determine if  
8 the plan will collect useful data to reveal  
9 unforeseen adverse events, other information  
10 necessary to protect the public health.

11 [Slide.]

12 The limitations that are most relevant in  
13 this situation are that the prospective  
14 surveillance period is limited by statute to 36  
15 months; it can be extended, but only if the  
16 manufacturer and the agency agree to extend the  
17 study period; and if the manufacturer and agency do  
18 not agree, then, before the agency could impose  
19 something longer than 36 months, the agency and the  
20 manufacturer would have to go through a dispute  
21 resolution process.

22 The criteria for a post-market  
23 surveillance study are that we can identify public  
24 health questions that are for cause because there  
25 has been an adverse observation or there have been

1 failures that have come up unexpectedly; new or  
2 expanded conditions of use--if someone were to  
3 take, say, a clinical lab device and suddenly move  
4 it into the home market for home use, that is a  
5 case where 522 studies have been required; or where  
6 the evolution of technology takes a quantum leap or  
7 has gotten so far away from the existing knowledge  
8 base that people are not really sure how it  
9 performs relative to the earlier generations.

10 In this process, we consider other forms  
11 of post-market surveillance methods other than  
12 direct patient follow-up-based studies.

13 Practicality and feasibility of conduct  
14 are taken into account when manufacturers are  
15 required to produce plans, and we have to be able  
16 to define how the data will be used. The priority  
17 in the decisionmaking process is the magnitude of  
18 risk and benefit.

19 That's the pre-packaged part of my  
20 presentation.

21 DR. YASZEMSKI: Thanks, Dr. McGunagle.

22 Dr. McGunagle, may I ask you how many  
23 times has post-market surveillance been used? Is  
24 it a frequent thing, an infrequent thing?

25 DR. MCGUNAGLE: It was more frequent in

1 the past. Currently, there are only two  
2 post-market surveillance studies that are actually  
3 ongoing. One of those is the plasma hip, because  
4 some of the manufacturers have chosen not to ask to  
5 be released from their obligation, so that's still  
6 going.

7           The other is on a clinical lab device that  
8 moved into home use. That one is just winding down.  
9 Now, in the past for short-term studies, 6 months,  
10 12 months, primarily lab bench or animal studies, I  
11 would say there have been about 8 to 10 post-market  
12 surveillance studies, but those were all relatively  
13 quick operations where we were looking at things  
14 you could do in a lab, things you could do in an  
15 animal model.

16           DR. YASZEMSKI: Dr. Finnegan?

17           DR. FINNEGAN: I know you guys don't even  
18 want to discuss this, but can you talk to us  
19 briefly about performance standards?

20           DR. MCGUNAGLE: That's not actually my  
21 bailiwick.

22           DR. WITTEN: Yes. That would be more in  
23 our area--performance standards is something where  
24 we would actually have to go through rulemaking and  
25 comment for. It is not a quick--it is not

1 something we could incorporate. There is no  
2 performance standard right now applicable to these  
3 products.

4 DR. FINNEGAN: But that is an option for  
5 us?

6 DR. WITTEN: Well, I think that in the  
7 history of FDA, there has only been one product  
8 that has had a mandatory performance standard.  
9 Maybe there has been more than one--let's say there  
10 is a handful at most--so it would be a major  
11 undertaking. But yes, that's something that you  
12 could recommend if you had a specific performance  
13 standard that you wanted to recommend.

14 DR. FINNEGAN: I guess my question is if  
15 you are looking at--if there is not enough data, so  
16 people are concerned about reclassifying, or if you  
17 reclassify what it states down here, that you have  
18 performance standards in place before the  
19 reclassification takes place, is that perhaps a  
20 more viable option for both patients and companies  
21 than not upgrading it--or downgrading it, or  
22 whatever you're talking about.

23 DR. YASZEMSKI: May I ask our Industry  
24 Rep, Ms. Maher, to comment on this?

25 MS. MAHER: I think the one concern that I

1 would see from industry and actually patient and  
2 even doctor's use on having performance standards  
3 is that as the state of the art changes, and things  
4 change, they would have to go through notice and  
5 comment rulemaking to be modified and changed, and  
6 notice and comment rulemaking is a very arduous  
7 process to go through. So it can't be fluid, and  
8 it can't change as technologies change.

9           A much better way to have the same  
10 information that I think you are looking for is  
11 through the use of guidance documents. There is  
12 law as to how guidance documents are developed.  
13 They get industry input, they get surgeons' input,  
14 they get panel input, and they can change in a much  
15 easier fashion, I guess, for want of a better word.

16           If you go through performance standards,  
17 20 years from now, the same performance standards  
18 will probably be sitting there on the books.

19           DR. YASZEMSKI: And I think that's where  
20 the total hip devices---as Dr. Witten mentioned,  
21 there are no performance standards in existence,  
22 only voluntary standards that we have heard about  
23 today, both from ISO and ASTM. Those can also  
24 change and can influence the guidance documents,  
25 which can also change.

1 Dr. Larntz?

2 DR. LARNTZ: Could I ask a question?

3 Essentially, one issue that I have, and I think it  
4 was brought up very clearly, is that depending on  
5 how much we depend on the clinical data, some of us  
6 feel that the clinical data are not adequate, or--I  
7 didn't say that; I'm wrong in there--someone would  
8 say that we feel that the analysis of the clinical  
9 data doesn't convince us that it is adequate. It  
10 could well be adequate if the proper analysis is  
11 done. And we would feel very comfortable, some of  
12 us, I'll say--me--down-classifying if I felt that  
13 the clinical data really did show the equivalence  
14 of metal-on-metal to metal-on-polyethylene. But I  
15 don't think they have demonstrated that because of  
16 inadequate statistical analysis of the data.

17 What do we do with that kind of dilemma in  
18 this situation?

19 DR. YASZEMSKI: I think that the decision  
20 today and the proposal today and the vote today are  
21 going to have to be done to each voting person's  
22 satisfaction based upon what they have seen and  
23 hear up to this point.

24 DR. LARNTZ: I understand that. What I am  
25 saying is in down-classification--and maybe I

1 should have paid more attention in my past--there  
2 is no such thing as a condition to be put on a  
3 classification. I mean, you can't give the agency  
4 guidance and say Class II if this analysis is done,  
5 and the results turn out to be reasonable.

6 DR. YASZEMSKI: I'll ask FDA for a  
7 clarification on that.

8 Dr. Witten?

9 DR. WITTEN: First, I'll say I agree with  
10 what you said, which is you're going to have to  
11 make your vote and your recommendations based on  
12 what is in front of you right now.

13 However, we do listen to our panel, not  
14 just to the vote and the number and what we get at  
15 the end, but to the discussion and what people say  
16 the issues are, so we'll certainly factor that into  
17 our decisionmaking. But there is certainly not, as  
18 far as I know, a conditional approval or something  
19 like that.

20 I just want to say one thing, and maybe I  
21 wasn't complete in my answer about performance  
22 standards. I don't think I gave you a very good  
23 answer, so I'm going to try again.

24 MS. MAHER: I have to tell you that Ms.  
25 Shulman gave us an answer this morning which was

1 "Don't even go there," so I apologize for going  
2 there.

3 DR. WITTEN: That's all right, but I want  
4 to give you another answer, anyway, if that's okay.

5 I just want to talk about the way that we  
6 use guidance and standards in case that isn't clear  
7 to everybody in terms of the review process,  
8 because it might make people feel a little bit more  
9 comfortable about the performance standards and the  
10 way that we currently control results.

11 That is that if there is a standard,  
12 whether it is a voluntary standard or it is in a  
13 guidance, that we are using in a review of the  
14 product, what we would do is if there is a product  
15 that fell outside of the range that we are familiar  
16 with, that sponsor would need to justify the  
17 differences between what they did and what was in  
18 the voluntary standard and explain why the product  
19 was still substantially equivalent.

20 In other words, it allows more flexibility  
21 in the substantial equivalence review than a  
22 mandatory performance standard would have. But if  
23 there are particular parameters or testing of  
24 concern, we still look at those results.

25 MS. MAHER: And you would develop guidance

1 specifically for this?

2 DR. WITTEN: What we do with your  
3 recommendations and with these reclassifications in  
4 general is if you all feel that there are controls  
5 available to provide reasonable assurance of safety  
6 and effectiveness, we take those controls that you  
7 all have identified--either from the petition or  
8 other things that you have added--and we put those  
9 all in a guidance document--I know that Haney or  
10 someone will correct me if I am not saying this  
11 right--but we put those all in a guidance document,  
12 and that would be our guidance document that would  
13 go along with the reclassification as the special  
14 control for that particular type of device.

15 MS. MAHER: I just have one other thing to  
16 add. Celia is absolutely right that when you are  
17 using the guidance documents, we as industry tend  
18 to follow them, and if we aren't going to follow  
19 them, we have to give a very good explanation as to  
20 why our design doesn't need to comply with that  
21 part of the guidance document during the 510(k)  
22 review.

23 I also just want to remind people that  
24 there are already a number of devices of this type  
25 on the market under the 510(k) process with the

1 clinical information that is currently available  
2 and that we are not looking at whether we are going  
3 to approve any specific device based on whatever  
4 clinical data was there, but whether these devices  
5 should be Class II or Class III and therefore,  
6 whether devices that are already out there would  
7 need to come back and go through the PMA process.

8 Thank you.

9 DR. YASZEMSKI: Thank you.

10 Thank you, both Ms. Maher and Dr. Witten.

11 I think perhaps what we can do now is go  
12 around the panel and try to answer the discussion.  
13 We have had a discussion from Dr. McGunagle about  
14 the post-market surveillance option. We have  
15 discussed a bit the performance standards. You see  
16 also on the list the possibilities of patient  
17 registries, device tracking, testing guidelines,  
18 and testing guidelines are one of the several  
19 things that were discussed in Mr. Steigman's  
20 presentation under the mechanical testing and the  
21 wear proposal. Also in his presentation, he listed  
22 voluntary standards and cited several ASTM and ISO  
23 standards and the guidance documents that we have  
24 just talked about.

25 So if I may, one of the leading ways of

1 addressing this issue of special controls is  
2 through using the several inputs that we have heard  
3 today in the realm of a guidance document, and I'll  
4 ask you to just think about that as you formulate  
5 your answer and give your opinion.

6 Dr. Aboulafia, may I start with you and  
7 ask you to answer Question 7: "Is there sufficient  
8 information to establish special controls to  
9 provide reasonable assurance of safety and  
10 effectiveness?" And if you answer "yes," please  
11 discuss what you think those controls ought to be.

12 DR. ABOULAFIA: I think there do need to  
13 be additional controls, so the answer is "yes," and  
14 to go about it in a little bit of a roundabout way,  
15 I think everything that Dr. Schmalzried said in the  
16 end sort of summarizes my feelings. That is, we  
17 can do additional bench-testing, we can do a lot of  
18 different things, and we really don't know how it  
19 is going to act clinically.

20 My major issue or question is how is it  
21 going to act clinically. Industry put together an  
22 excellent, well-organized bit of information that I  
23 think is honest and straightforward; the study  
24 design is well-done. I have no objections to any  
25 of that. The only issue I have is that there is

1 not enough information yet.

2 To put it another way, I think the  
3 submission is premature. There were 97 patients in  
4 the metal-on-metal that are 2 years or more and 66  
5 in the control group--that's not true--129 and 88,  
6 respectively. I think those numbers are too small.

7 So the special control I would want is to  
8 see follow-up data on a study that is already in  
9 progress, and I think that would address my  
10 concerns without being onerous on industry.

11 DR. YASZEMSKI: Thank you, Dr. Aboulafia.

12 Dr. Peimer?

13 DR. PEIMER: I am cognizant of the fact  
14 that anything we recommend here is going to  
15 actually carry over into the metal-on-polyethylene  
16 devices, because if manufacturers of metal-on-metal  
17 or any other prosthesis are accumulating data or  
18 adhering to standards or performance that seem to  
19 have a good outcome, then others are going to want  
20 to at least compare themselves to those outcomes  
21 and show how they are as good or better.

22 So I think that taking the view that  
23 things are already out there under the current  
24 guidelines doesn't necessarily absolve putting  
25 additional controls on this from that perspective.

1 I would agree that we need additional  
2 long-term data, but I don't know which of these  
3 controls would best get us those data. From my  
4 ability to understand, I would think both patient  
5 registry and device tracking are items that will  
6 give us the long-term information.

7 I would very much like to see these  
8 studies go out to a 5-year time with a large number  
9 of patients, because most of the failures don't  
10 occur in the first 2 years, except for the really  
11 gross ones.

12 So I think my struggle is that this  
13 mission is, to quote my colleague, a bit premature  
14 based on the information we have. However, it will  
15 reflect a number of issues. I would like to see  
16 the device tracked and the patients tracked  
17 longer-term.

18 DR. YASZEMSKI: So I take it your answer  
19 to the question is "yes," with those two--

20 DR. PEIMER: It is "yes," right.

21 DR. YASZEMSKI: One of the ways to address  
22 the fact that the long-term data is lacking is to  
23 include that in the labeling as it goes out, once  
24 we get to labeling, to say that long-term data is  
25 not yet available.

1           Let's go on to Dr. Li. Dr. Li?

2           DR. LI: I think my answer to the question  
3 is yes. I think there are a lot of unanswered  
4 questions about the metal-on-metal devices that are  
5 probably not going to be found out in a 2-year  
6 period. I think a 2-year period just tells you if  
7 you have a really bad device, and it actually  
8 doesn't do anything to tell you if you have a good  
9 long-term device.

10           So I would like to see post-market  
11 surveillance. I would really like to see patient  
12 registry device tracking--but those aren't really  
13 sensible suggestions, I don't think, as they are so  
14 difficult to get going.

15           The testing guidelines--would this improve  
16 the bench-testing--is that what that means?

17           DR. YASZEMSKI: Yes; whatever you feel  
18 would be appropriate.

19           DR. LI: Without reiterating the list, I  
20 think those suggestions that we talked about a few  
21 minutes ago on how to do the hip simulation  
22 testing, I think I would put in as testing  
23 guidelines.

24           I guess the issue there is that although  
25 it doesn't have a direct clinical tie versus what