

1 DR. HOPE: In Australia and I believe also in the  
2 States, the only places that can actually receive the  
3 product to use it are accredited for handling therapeutic  
4 isotopes. This is locked down in the Code of Federal  
5 Regulation, which means they already have in place their own  
6 particular procedures for dosage measurement, verification,  
7 and delivery.

8 We also have in place a training program to make  
9 sure our particular product is understood by anybody who is  
10 a new user, so that we make sure our particular product is  
11 taken into account and put into their system.

12 MR. AYRES: A follow-up question to that, is the  
13 training program part of your required, if you would,  
14 labeling, or were you recommending that be required for all  
15 new customers or institutions?

16 DR. HOPE: I am sorry, the training, yes.

17 MR. AYRES: Are you requiring the training for new  
18 institutions that enroll?

19 DR. HOPE: Yes.

20 DR. GRAY: Perhaps I could just expand on that.  
21 Absolutely, there is quite an extensive training program  
22 that everyone must undergo before the product is released.

23 MR. AYRES: I would certainly think so.

24 DR. MALCOLM: Yes, Dr. Mehta.

25 DR. MEHTA: This is my last question. Are there

1 any data on response rates from non-radioactive spheres,  
2 because after all, this is an angiogenic occlusive  
3 methodology?

4 DR. GRAY: Not in humans, but there certainly are  
5 in animals, and we did this many years back, and, in fact,  
6 you do see an effect if you embolize with cold spheres. If  
7 you take animal studies, randomized animal studies, and  
8 embolize tumors with cold spheres, you will see an anti-  
9 tumor effect, but it is very transient, and within a matter  
10 of days, the tumor is responding and growing again, whereas,  
11 if the particles are radioactive, then, you see continued  
12 regression, very much so.

13 DR. MALCOLM: I think we will move on unless there  
14 are some other questions.

15 These are several questions that we would like to  
16 put forward as discussion points for this PMA.

17 Please discuss the PMA data as it pertains to  
18 providing the valid scientific evidence needed to conclude  
19 that SIR-Spheres is safe and effective for the treatment of  
20 metastatic colorectal tumors in the liver.

21 Are there data to support the use of SIR-Spheres  
22 for the treatment of all (primary and secondary) malignant  
23 liver tumors, not just colorectal metastases?

24 If I could have your comments.

25 DR. GRAY: The panel pack only referred to

1 patients who were in our Phase II and our pivotal study with  
2 colorectal metastases. We have quite a deal of data that  
3 has not been published on non-colorectal metastases, so one  
4 cannot make a judgment on that because it hasn't been  
5 presented.

6 We did include in the PMA application substantial  
7 supporting data coming from a number of scientific  
8 publications on the use of SIR-Spheres in primary  
9 hepatocellular carcinoma, and we believe that the response  
10 data and the survival data strongly supports the findings  
11 that we have reported in colorectal cancer.

12 Apart from that data, the only two diseases that  
13 we have provided a significant amount of data on, but we  
14 think that they are very complementary.

15 DR. MALCOLM: Any comments or questions from the  
16 panel members concerning the response or the question?

17 DR. GARRA: Dr. Toledano, don't you have anything  
18 to say about this?

19 DR. TOLEDANO: So, it's Toledano again, the big,  
20 old meanie. I have some concerns about the safety and  
21 efficacy data. First, on the safety data because I know  
22 that there is only a limited number of patients for whom  
23 this would be indicated, this device would be indicated, but  
24 the PMA report on 400 patients total, I think, over eight  
25 years, you said you have experience on 700 patients total.

1           We have just heard that the FDA would only  
2 consider this PMA with the infusion set, and that you said  
3 would knock out 25 percent of those patients, so that is  
4 goodly number of patients, but certainly not enough to  
5 address any sort of unpredictable toxicities or adverse  
6 events that would happen with widespread use.

7           I do have some concerns about what would happen  
8 when the SIR-Spheres are used in a broader population.  
9 Also, in terms of the efficacy, really, the only  
10 statistically significant thing that I see that is robust to  
11 the small numbers and everything is a delay in the time to  
12 liver progression. So, that is certainly an efficacy  
13 endpoint, but I wouldn't hang my hat personally on the  
14 response rate data.

15           I think there is a lot of promising things with  
16 the SIR-Spheres, but as far as effectiveness, the only thing  
17 I see as being proved is an increase in time to liver  
18 progression.

19           DR. MALCOLM: Dr. Mehta.

20           DR. MEHTA: I would like to comment specifically  
21 on the efficacy endpoint. This is clearly a very, very  
22 difficult endpoint, difficult disease to deal with, and the  
23 endpoint also is quite difficult in the sense that these are  
24 not patients that are routinely going to be cured, so  
25 obviously, if we can delay events in these patients, it is a

1 good thing, but these events have to be meaningful events.  
2 They can't just be responses on CT scans.

3           These are to be events that affect the patient,  
4 and I am not sure that I saw data that convinced me that a  
5 delay in liver metastasis and improvement in response meant  
6 something to the patients. In fact, as best as I recall  
7 hearing the data on quality of life, I was told the quality  
8 of life can go in only one of two directions, either worse  
9 or the same.

10           So, if we can't improve survival, and the quality  
11 of life data can't be affected in a better fashion, I am not  
12 sure I understand the total impact of a radiographic  
13 response on a patient.

14           DR. GARRA: I would like to make a comment, maybe  
15 the manufacturer would, too. I kind of view this a little  
16 differently. My cousin died of colorectal cancer  
17 metastases, and I think it is a little different when you  
18 have somebody that is affected by it. I was interested in  
19 the small percentage of patients who might be cured, and it  
20 will take forever to get statistically significant numbers  
21 on that, but that is very meaningful, that is very  
22 meaningful information.

23           The time to progression is very meaningful. We  
24 have a member of our department who has pancreatic cancer  
25 with liver mets. She is declared unresectable because of

1 the liver mets, and you have to wonder, with a technology  
2 like this, whether that would necessarily be the case, and  
3 for her, every month of delay is very important.

4 So, I think that the data that the manufacturer  
5 has presented is very meaningful. It doesn't appear to be  
6 statistically in some cases, but I know it is a very  
7 difficult disease and people are looking for small changes  
8 here. They are not after a cure, they just want a little  
9 more time.

10 It looks to me like they have made that case, at  
11 least in my opinion.

12 DR. HARMS: I would agree with that, and the other  
13 key point here is the safety data seems to be very good. A  
14 lot of the treatment for this disease has pretty severe  
15 morbidity, even death, with liver resection, and if this  
16 agent is effective in treating the liver metastases and  
17 relatively safe, I would be in favor of that treatment.

18 DR. MALCOLM: Any comments from the manufacturer  
19 on the comments that were made?

20 DR. GEBSKI: If I could just comment as far as my  
21 experiences with things like quality of life and perhaps  
22 response. Response certainly is one of the main sort of  
23 almost primary endpoints most medical oncologists use to  
24 look at efficacy of most pharmaceutical drugs that they use.

25 It is also very difficult. You really need lots

1 of numbers, hundreds of patients to get enough data down the  
2 track to be able to get the regular CT scans to make the  
3 area measurements and to try and get an estimate of really  
4 what is going on.

5 I think part of the Phase III study, the fact of  
6 having to prematurely terminate it before the 95 patients  
7 made this whole exercise a little bit harder. The patients  
8 really didn't -- a bit like the example we heard -- they  
9 really wanted something, and it was very difficult then to  
10 sort of continue with the hard influence of survival and  
11 even response to some extent.

12 With regards to the quality of life, I think that  
13 also needs to be mentioned. Quality of life back in 1991,  
14 when this started, was a very different perception of what  
15 we would get from patients to what we get now in the year  
16 2000. So, it is difficult to look at what was collected and  
17 how it was collected and how it was analyzed back then or  
18 would have been analyzed back then, and the quality of life  
19 was really not the primary sort of emphasis.

20 The curative effect was what people were trying to  
21 get. The quality of life was trying to treat the patient,  
22 not just the disease. I think quality of life, the emphasis  
23 currently is much, much more detailed, and so I think we  
24 should also keep that in that form of perspective.

25 DR. GARRA: I would like to make a comment. For

1 me, the gains shown here, I think they will prove to be  
2 larger as larger numbers of patients are done and the  
3 techniques refined a bit more, but for me, people will go  
4 after even a small improvement when they are in a terminal  
5 illness situation.

6           So, the issue here is really a safety issue, I  
7 think primarily, is this material safe. Dr. Harms already  
8 mentioned that most of the other therapies we have are  
9 pretty drastic, and aren't very pleasant to go through, and  
10 this is relatively benign compared to some of them,  
11 especially if you do it through a femoral artery catheter.

12           So, I think the issue Alicia was concerned about,  
13 Dr. Toledano was concerned about method of delivery, and I  
14 think the delivery is going to be the only risky part here.  
15 If the person is poorly trained, if they let the catheter  
16 drop out into the gastroduodenal artery or left gastric  
17 artery while the material is being injected, you are going  
18 to have serious problems, but I don't think it is going to  
19 be in the delivery system, I think it is going to be errors  
20 on the part of the person who is doing the procedure.

21           I don't know of any way, we don't really have a  
22 good way of controlling that even now. You stop referring  
23 to somebody who makes mistakes like that. I wonder if the  
24 manufacturer has considered safeguards in that respect.

25           DR. GRAY: Yes, you are absolutely right. You do

1 need a very skilled and very careful interventional  
2 radiologist. I think that is an extremely important point.

3 It is our intention as part of our training  
4 program that we will only allow institutions to have access  
5 to this device who are adhering to standards that we would  
6 accept, and that would involve personal supervision of the  
7 radiologists during the training period.

8 DR. GARRA: Is that something that is practically  
9 feasible given manpower constraints?

10 DR. GRAY: Yes, I think it is. We have already  
11 done that in Asia. In fact, it was our intention to recruit  
12 five centers in the United States initially and to use those  
13 as training centers themselves.

14 DR. TOLEDANO: One of the recurring questions when  
15 I was reviewing the panel pack that we got was whether I was  
16 focusing on the SIR-Spheres or the SIR-Spheres plus the  
17 delivery. I had actually decided just before the FDA said  
18 that it was both, that it was just the spheres themselves.

19 So, I would just urge the sponsor and the FDA to  
20 really think carefully and speak together at great length as  
21 to whether this PMA is just the SIR-Spheres or whether it is  
22 the SIR-Spheres plus the infusion set, because that seems to  
23 be a recurring question.

24 DR. MALCOLM: Dr. Mehta.

25 DR. MEHTA: I just wanted to follow up on the

1 actual methodology question because I think that is where  
2 the real crux of this thing will arise if it is widely  
3 practiced.

4           We realize that the toxicity has been low, but  
5 there is a very good reason for that. The data that we are  
6 seeing are primarily presented by users who are  
7 sophisticated and perhaps the world's most experienced users  
8 in this methodology. It is no wonder that the complication  
9 rates are low.

10           However, once the method is exported, the  
11 likelihood for complications rises substantially. For  
12 example, will we mandate the use of vasopressors in all  
13 patients, will this be a mandatory part, will this be part  
14 of the package to ensure that more of it goes into the tumor  
15 as opposed to normal liver?

16           Will we mandate that a macro-aggregated albumin  
17 scan be done in every patient prior to this? That means  
18 that a patient goes on the interventional radiology table to  
19 get a catheter placed. They then go to Nuclear Medicine to  
20 get a scan. They come back to get a vasopressor injected.  
21 Then, they actually get the microspheres.

22           Is this going to be the methodology that is going  
23 to be labeled?

24           DR. GARRA: I think they could use a portable  
25 camera.

1 DR. GRAY: Absolutely. The use of the MAA scan is  
2 an absolute requirement before use of the product. There  
3 would be no doubt about that at all in order to ensure that  
4 there was no overdosing of the lung, for instance. We have  
5 never seen radiation pneumonitis, but there have been five  
6 cases seen in Asia, three of which were fatal. These were  
7 in the early days, and they were before the development of  
8 the partition model, and without the adequate use of  
9 safeguards, such as the lung breakthrough level. So, that  
10 would be an absolute requirement.

11 There is not an absolute requirement to use  
12 vasoconstrictors. The reason the vasoconstrictors got into  
13 the Phase III trial was that in the late 1980's, we had  
14 animal data to show that we could redistribute blood more  
15 favorably by the use of vasopressors, and there is a whole  
16 series of vasopressors that you can use.

17 Subsequent to that, there has actually been a  
18 study showing--again, this comes out from our colleagues at  
19 the Chinese University--showing that in patients, it doesn't  
20 seem to make any difference, but because it was written into  
21 the trial, we kept it there.

22 DR. MALCOLM: I was just going to try to summarize  
23 what I think I heard concerning this question, so we are all  
24 on the same page. For this question, I surmise the  
25 following. Number one, that it appeared at least from the

1 data presented, even though they are small numbers, that  
2 this device can be utilized in a safe manner. That is one.

3 Two, there were also concerns that in order to try  
4 and assure that the device was delivered in a safe manner,  
5 that certain criteria must be met, that is, to try to train  
6 and have experienced persons delivering the device initially  
7 and having training centers.

8 Next, was that the patients go through what has  
9 been described in the PMA, the MIAA study, make sure that is  
10 also within the requirements, and that consideration or  
11 perhaps it should be a must that appropriate  
12 vasoconstrictors be utilized at the time of the  
13 administration. I heard that.

14 The other thing that I heard was that the data is  
15 limited, I think we all admit that, that from the small  
16 numbers, from the variety of patients and administration of  
17 the device, that there are some questions about the  
18 statistical evaluation of the data, but that it does appear  
19 to help some patients and perhaps in some circumstances it  
20 has led to the fact that some patients have perhaps even  
21 gone to the point of resection or curability, and it does  
22 appear to increase some patients' time to progression,  
23 although overall the survival has not significantly been  
24 changed.

25 The quality of life issues are still somewhat in

1 question, but it did not appear to increase or decrease a  
2 patient's quality of life, and not make a significant  
3 change, although if looked at further today, that might give  
4 us some more information.

5 Did I summarize that okay? Did I miss anything?

6 DR. GARRA: I would just say with regard to  
7 whether the scientific evidence is convincing enough, I  
8 would say we are sort of divided on that. Some people think  
9 it is on very thin ice, and others of us are a little more  
10 comfortable with it, but maybe Alicia and Dr. Mehta will  
11 address that.

12 DR. TOLEDANO: I would like to comment and then I  
13 will let Dr. Mehta comment. I think that if we focus really  
14 on the increase in time to liver progression, we are on  
15 really nice safe ice, and so that is what I would focus on,  
16 on what we do have and what we do know, and from Dr. Garra's  
17 recounts and Dr. Malcolm's remarks, that these are important  
18 endpoints. Something like a delay in time to liver  
19 progression is an important clinical outcome for a patient.

20 So, that is what I would focus on for the  
21 effectiveness data.

22 DR. MALCOLM: Dr. Mehta.

23 DR. MEHTA: I am still a little concerned about  
24 the efficacy data, and I am concerned because we are only 20  
25 patients short of showing a 30 percent improvement in

1 survival, a remarkable endpoint, and yet we abandon the  
2 trial to try and show this 30 percent improvement, and since  
3 we abandoned it, we are now fishing for other endpoints.

4           The two primary endpoints of the study, if we look  
5 at what the study started off with are negative, and we are  
6 left with secondary objectives that we are now trying to  
7 turn into positive because we never finished the trial in  
8 the first place, and that concerns me.

9           DR. MALCOLM: Good point.

10           DR. GRAY: Could I comment on that? I think that  
11 is quite true. In terms of quality of life, the quality of  
12 life for patients having hepatic artery chemotherapy is, in  
13 fact, very high. It is a form of chemotherapy that is very  
14 well tolerated with very few systemic side effects.

15           It would be impossible for us using a trial that  
16 used the same chemotherapy in both arms to improve quality  
17 of survival. It just would be not possible, and that is not  
18 what the trial was to determine.

19           It was to determine whether there was any loss of  
20 quality of life with the addition, and I think that case has  
21 been proven.

22           DR. MALCOLM: Dr. Mehta.

23           DR. MEHTA: I think one can get into an  
24 unnecessary debate about this in the sense that if the  
25 quality of life cannot be improved on these patients, and

1 median survival improves by less than a month, why are we  
2 treating patients if their quality of life can't be  
3 improved.

4 DR. GRAY: That is to a median survival. The  
5 median survival improvement is modest because there is a  
6 large cohort of patients of approximately 50 percent who  
7 developed a systemic disease that original treatment can't  
8 have any effect on, and it is very difficult at the  
9 beginning to find out how to identify that cohort of  
10 patients and exclude them.

11 If we look at the patients that, in fact, don't  
12 get disseminated disease, then, we do see a significant  
13 survival improvement, as well. Now, that is a post-hoc  
14 analysis and, of course, it is subject to all the criticisms  
15 of post-hoc analyses.

16 But I think that your statement really  
17 oversimplifies the survival benefit that you do see for  
18 certain subgroups of patients, and they are the ones that  
19 don't develop extrahepatic disease, and that is a big  
20 subset. It is almost 50 percent of the patients.

21 So, the mean survival--and I agree there is  
22 weaknesses in mean survival--is improved to the order that  
23 the mean survival in treated patients is nearly two years.  
24 Now, it is not median, it is mean.

25 DR. MEHTA: Does that mean that as part of the

1 approval, you will ask that patients be worked up to  
2 demonstrate that there are no extrahepatic metastasis before  
3 this therapy is offered, because if there was extrahepatic  
4 metastasis, it appears not to help them. So, that will be  
5 one of the exclusion factors built in.

6 DR. GRAY: Yes, it would, and that would be part  
7 of our recommendation, that we would caution any clinician  
8 from using a regional treatment in the presence of  
9 widespread disease.

10 It is a clinical judgment, but we already do  
11 caution against that.

12 DR. MEHTA: That is a caution or an exclusion?

13 DR. GRAY: At the end of the day, I think it is up  
14 to the clinician himself to decide whether or not it is  
15 likely that the patient will get benefit. A common clinical  
16 scenario is that you will see a patient that has very  
17 extensive live metastases and one, small 2-millimeter nodule  
18 that is suspicious and probably is a metastasis.

19 Now, that patient we would say is likely to  
20 benefit if, in fact, the disease in the liver can be  
21 contained. So, in that scenario, we would use our clinical  
22 judgment and say that that patient would be suitable for a  
23 form of regional treatment.

24 Another case would be a patient that had extensive  
25 disease in multiple sites. In that situation, any sort of

1 control in the liver is unlikely to translate into patient  
2 benefit, and therefore we wouldn't recommend it.

3 At the end of the day, I think it is the clinician  
4 that has to make that judgment, and we do that all the time  
5 in recommending regional systemic treatments.

6 DR. GARRA: I would just like to remind the panel  
7 that should the FDA approve it, the clinician will be able  
8 to call, make the decision on which patients to use it on,  
9 and your labeling may indicate that it is only indicated for  
10 a patient where there is no evidence whatsoever of a  
11 metastasis, but if a clinician decides it is in the best  
12 interest of their patient to use it on somebody who does,  
13 then, they would be able to do so.

14 DR. VISHNUVAJJALA: I just want to respond to the  
15 comment by Dr. Mehta, about the trial being abandoned and  
16 what would have happened if the 95 patients had been  
17 accrued.

18 The 95 patients come from an expected survival of  
19 the treated arm of having about 80 percent. That actually  
20 did happen, and the reason it is not statistically  
21 significant is because the control arm did just as well.  
22 So, you are not going to have a significant difference, and  
23 I think that probably wouldn't change if it went from 74 to  
24 95.

25 So, in that regard, the trial stopping at 74 did

1 not have much of an effect. I mean this is just my opinion  
2 looking at the data. If they had all 95 patients, they  
3 still wouldn't have had statistical significance, but having  
4 more patients is always better, but as far as statistical  
5 significance, it wouldn't have made any difference.

6 DR. MEHTA: I would agree with that, but in my  
7 experience not as a statistician, but as a clinician working  
8 on clinical trials, that is not how stopping rules are  
9 designed for clinical trials.

10 DR. VISHNUVAJJALA: No. I mean this is just a  
11 comment about what would have happened to the statistical  
12 significance. That is why I said, you know, having more  
13 patients is better.

14 DR. GEBSKI: If I could just comment on that.  
15 This wasn't a stopping rule. It was a trial that found  
16 accrual very difficult. I think prior to a lot of these  
17 formal statistical rules being sort of grabbed into clinical  
18 trials, lots of trials were curtailed, if you like, based on  
19 just practical issues, and one of them is accrual.

20 I think that may have been sort of missed in that.  
21 This wasn't interim analysis, it was purely based on  
22 primarily that the patients were offered something that they  
23 felt was going to benefit them, and it made randomization to  
24 the control arm extremely difficult.

25 It was then a matter of then using the statement

1 that the FDA sort of put out, accepted other things, such as  
2 surrogates, such as response, et cetera, and time to  
3 progression, that sort of enabled us to sort of put it all  
4 back together using that.

5 DR. GRAY: Can I just expand on what Dr. Gebski  
6 has said? I mean part of the reasons are as he has said,  
7 but part of the reason was because of the statement in March  
8 1996 by the FDA entitled Reinventing the Regulation of  
9 Cancer Drugs, and it is under the subheading of Faster  
10 Approvals, and I read to you, "In order to speed up the  
11 entire process further, FDA is adopting a uniform policy to  
12 permit accelerated approval of a significant number of new  
13 cancer therapies," and then it goes on, "because of this  
14 experience, FDA believes that for many cancer therapies, it  
15 is appropriate to utilize objective evidence of tumor  
16 shrinkage as a basis for approval."

17 That was another reason why we thought it was  
18 appropriate in view of the cost implications of continuing  
19 the trial and the difficulty of accruing patients together  
20 with this statement by the FDA. They were very legitimate  
21 stopping rules.

22 DR. GARRA: Can I just make a comment here at this  
23 point? As has been pointed out to me, this discussion  
24 session is primarily for the panel to discuss among  
25 themselves, and we can ask questions of the manufacturer,

1 but the manufacturer should be responding to our questions,  
2 so we will try to limit that because we want to move ahead  
3 with some of the other questions.

4 MR. AYRES: Are you going to address the second  
5 part of that question?

6 DR. GARRA: We thought we already had.

7 DR. MALCOLM: Actually, I made my comments on the  
8 first part. The second part, I thought we had, and the  
9 comment was that there were some data, but that data was not  
10 submitted to us in regards for primary data. That has been  
11 submitted to us really for secondary or metastatic disease.

12 Number 2. Please discuss whether the labeling of  
13 the device including the indications for use is appropriate  
14 given the data provided in the PMA application. Please  
15 comment specifically on the indications, contraindications,  
16 warnings, and precautions.

17 I think we actually in Question 1, we talked about  
18 some of the questions about, not necessarily precautions,  
19 but labeling of the device and utilizing vasoconstrictors,  
20 ensuring that we had the MIAA study performed. We talked a  
21 little bit about that, I think, just a few minutes ago.

22 A little bit about indications, which is kind of  
23 fuzzy, I think, we just talked about in regards for  
24 metastatic disease, for which patients would be a clinical  
25 decision. Contraindications, we haven't really discussed in

1 any type of detail.

2 DR. GARRA: I would like to make one comment if I  
3 could. I noticed that ascites, even a trace of ascites was  
4 listed as a contraindication, and I was a little unclear as  
5 to why that was listed. Maybe I misread it, but I thought  
6 it was in there.

7 DR. GRAY: Yes, it was in there, because that  
8 would be indicative of terminal liver failure, the  
9 expectation of a patient with widespread disease in their  
10 liver who has ascites would have a life expectancy generally  
11 of the order of weeks, and it would be inappropriate in our  
12 view to treat that patient because it is likely that the  
13 liver function would deteriorate before it would, in fact,  
14 improve, and that that might result in premature death.

15 DR. GARRA: Do you think--and maybe Dr. Mehta can  
16 answer this, too--but it has been my experience there are  
17 many, many causes of ascites in an ill patient like this  
18 including reactions of various drugs, other things,  
19 including tumor involvement on the surface of the liver,  
20 which might cause weeping into the peritoneal cavity.

21 So, I would think that maybe ascites alone without  
22 any other indications of liver failure might be a little bit  
23 strict. I would just like to hear the comments of some of  
24 the other clinical members on the panel on that.

25 DR. MALCOLM: I agree. That is a comment I was

1 saying to him I couldn't quite--referring to the fact that  
2 just because you have ascites, because again, as indicated,  
3 there are multiple reasons for ascites, not necessarily that  
4 the patient has end-stage liver disease.

5 DR. MEHTA: I think I agree with the two of you in  
6 the sense that there is ascites and there is ascites. I  
7 think that people who clearly are in liver failure or they  
8 are about to die, they have got extensive disease, they  
9 obviously are not going to benefit from any therapy.

10 But then you have the occasional patient that has  
11 just a very tiny amount of ascites that may be directly  
12 disease-related or not. It also depends on how you look for  
13 it. If you look for it by good old physical exam, you are  
14 going to miss a lot, you know, and if you look for it with  
15 ultrasound or CT, you are going to pick up a whole lot more.

16 Again, as you pointed out, if this is approved,  
17 the using physician will ultimately decide who the selected  
18 patient is. So, I am not too concerned about that.

19 I have a question about the contraindications,  
20 warnings, and precautions category, and that is because all  
21 the data that we have seen are data that are relevant to  
22 intrahepatic arterial administration of FUDR, which at least  
23 in the United States is a relatively rarely practiced form  
24 of chemotherapy for patient with colorectal metastasis, and  
25 certainly outside the context of some of the larger academic

1 institutions, this is far less common.

2           The most frequent form of chemotherapy that is  
3 administered for these patients is systemic intravenous  
4 chemotherapy, and, in fact, probably based on the recent New  
5 England Journal of Medicine article, it is going to be  
6 irinotecan and 5-FU. Irinotecan and 5-FU are both  
7 radiosensitizers.

8           Irinotecan is a potential hepatic radiosensitizer,  
9 and we haven't seen any data with the use of yttrium  
10 microspheres with this application, which is likely to be  
11 the most common sequence to be used in the U.S., and I have  
12 some concerns about that.

13           DR. GARRA: I think the manufacturer had even  
14 mentioned that the most common therapy these days would be  
15 systemic chemotherapy, possibly in such combination, and  
16 given the fact that maybe numberswise we don't have a lot of  
17 patients, that you might consider at least a small-scaled,  
18 post-approval study to look at some of these issues that  
19 with a changing of the chemotherapy, will that affect a  
20 liver toxicity and things like that, and also we would get  
21 the numbers up on other tumors, as well.

22           Were there any other--I mean I had the issue about  
23 the ascites, otherwise, I was okay on the labeling issues--  
24 indications and contradictions? Are there some that other  
25 people were concerned about?

1 MR. AYRES: I had a couple that I guess come under  
2 warnings and information. I found, at least in the panel  
3 pack, there was no dosimetry information, in other words,  
4 exposure rates, which I think would be particular important  
5 from a couple of aspects.

6 One is accident conditions where the material goes  
7 the wrong place and you need to really calculate the dose.  
8 The other is--and I understand with IDE studies, a nice,  
9 fixed system of a certain number of millicuries per amount  
10 of liver involvement--but with increased patient use and  
11 more sophisticated dosimetry, one could probably do a better  
12 job of tailoring the dose to the amount of tumor involvement  
13 of the liver with appropriate dosimetry.

14 That was one, an amazing lack of dosimetry in at  
15 least the panel pack. I understand it is in the literature,  
16 but it should be in the labeling information and available  
17 to the users.

18 The other one was there is no information--and I  
19 brought this issue up a little bit earlier--on the dose  
20 rates, exposures that one would receive from handling the  
21 device, the infusion apparatus, the shipping container, the  
22 plastic system when you are inserting needles, so that  
23 radiation protection personnel could properly protect and  
24 plan for the infusions of these patients, so I don't see any  
25 of that radiation protection exposure rate information in

1 the labeling, which I think should be there.

2 DR. TOLEDANO: I have another comment. In the  
3 labeling, it says that the spheres are 20 to 40 microns in  
4 diameter, and in the device description, it states that they  
5 are 30 to 35 microns, and we heard about how important size  
6 was in terms of getting the spheres to where they are  
7 supposed to be, but not beyond that.

8 I just wondered from some of the clinicians on the  
9 panel, is that within an acceptable range or is that  
10 something that we need to worry about or not?

11 DR. MALCOLM: I just think it needs to be  
12 clarified. My assumption was between 20 and 40, but I  
13 missed that 30-35, maybe I just didn't see it. I don't have  
14 any concerns about that, I think it was within that range.  
15 I think it does fit the anatomy and what was discussed, and  
16 it has been demonstrated, I think, in the patients that  
17 received the spheres, that there was not a problem.

18 I noticed, I think it is just little things that  
19 are different here versus Australia, in some of the  
20 comments. I don't remember the page which it was on in  
21 regards for the patient's information. I have to admit to  
22 you in this country, we are a lot more stringent or have a  
23 lot more detail on potential toxicities and alternatives in  
24 therapy. This was a little scant, but I am sure that can be  
25 resolved with the patient consent form, but this consent

1 form was not the standard one we have here. I don't know if  
2 other people noticed that, it was pretty brief. Our has  
3 significantly more detail, but I think that is a minor issue  
4 that can be resolved with the FDA and Regulatory Commission,  
5 but I did notice that when I read through the document.

6 Any other comments on Question 2? I think if I  
7 summarize that one, what I heard was there were still some  
8 questions on dosimetry and handling that we wanted to try to  
9 resolve and get into the packet.

10 As far as other issues, discussion about ascites  
11 and really up to the clinicians to make decisions,  
12 otherwise, I don't think there were any significant  
13 additional comments. Did I say that okay?

14 Let's go to Question 3. If approved, should the  
15 sponsor be required to conduct post-approval studies to:  
16 (a) address any outstanding safety issues, or (b) further  
17 evaluate effectiveness based on improved survival time  
18 and/or Quality of Life, or (c) other.

19 I think some of the comments that were made about  
20 post-approval studies just a few minutes ago by Dr. Garra in  
21 regards to looking at the new data that is coming out, in  
22 regards to utilizing other agents, systemic chemotherapy,  
23 and its potential effect on utilizing this device. I think  
24 that was discussed, so that is one issue that has already  
25 come forward. Are there others?

1 DR. MEHTA: I will play the devil's advocate.  
2 Let's say we ask for a post-approval study. The only hard  
3 endpoint we have here is delay in intrahepatic progression.  
4 What would we consider unacceptable as a result from that,  
5 that would result in withdrawal of the drug from the market?

6 For example, let's assume that the results are  
7 positive because of a statistical quirk, we just have a  
8 better group of patients in one arm, and that is why they  
9 look good on the limited number of patients we have.

10 Then, we do a post-approval study, 5,000 patients  
11 get treated worldwide. Time to progression in the liver is  
12 X number of months, which is much less than what is reported  
13 in the initial Phase III study. What happens then? Is that  
14 good enough, is that not good enough?

15 DR. GARRA: I guess it depends on how the study  
16 is--you would be comparing it with another arm that is going  
17 to have a different therapy, as well, so that both arms may  
18 have a different time to progression. So, I guess you would  
19 have to compare them.

20 DR. MEHTA: But that would require a Phase III  
21 study. If we didn't require a Phase III study, if we just  
22 monitored patients that got the therapy.

23 DR. GARRA: I guess I am not concerned about that.  
24 What I am personally concerned about is the issue you  
25 brought up was is there a safety hazard, are you going to

1 sensitize the normal liver by using a systemic chemotherapy  
2 drug. I think it is not likely, but I think it is something  
3 that would be a focus of a post-approval study for me.

4           It is a matter of our outlooks. I am looking at  
5 it like I think it is going to be successful, and I think it  
6 is going to lengthen survival, as well, and you are looking  
7 at it, it might not it might make it worse, and we will  
8 probably have to consider that.

9           DR. MALCOLM: Additional comments, questions? Any  
10 outstanding safety issues? I am going to bring it up again  
11 to make sure. Okay.

12           DR. GARRA: Just one other comment. This is the  
13 point, if we are going to do it at any point, we had figure  
14 out if there were going to be a post-approval study, what  
15 would we monitor.

16           Obviously, complications like radiation hepatitis  
17 would be one, but what else, what should be the endpoints?

18           DR. MEHTA: I think we have a statistician, so we  
19 should really ask the statistician, but I think my concern  
20 is that if we look at response rates or intrahepatic  
21 progression in a systemic chemotherapy cohort, we don't have  
22 data to compare with, so that almost brings us to a Phase  
23 III study, unless we use historic data, say, for example,  
24 from the last New England Journal, the Irinotecan Working  
25 Group study cohort.

1 DR. GARRA: Well, if that is a valid study, that  
2 would be one way to go.

3 DR. MEHTA: That means you have two different  
4 companies, and we ought to get data from two companies, and  
5 does that work.

6 DR. GARRA: FDA might be able to do it, I don't  
7 know.

8 DR. TOLEDANO: I think we have to say welcome to  
9 the wonderful world of observational studies. I think one  
10 thing that this sponsor has learned through their experience  
11 in Australia and in Asia, is that the patients are coming  
12 with referrals for the spheres, and the patients want them.

13 There is this slim chance there is something good  
14 that is happening, and they want it, they want it whether  
15 they are going to be the 1 in 20, or the 1 in 10, or the 1  
16 in 5, or the 1 in a million, they want that chance.

17 So, I don't think that a Phase III trial is  
18 workable. I don't know that we could get sufficient numbers  
19 of accrual, and even if we could, I don't think the patients  
20 would be willing to be randomized.

21 So, we are going to have to deal with something  
22 observational. In that sense, I think it is just really  
23 important to be able to make sure that we collect adequate  
24 data on several different endpoints and on several different  
25 patient characteristics, and information about training,

1 information about delivery systems, that we can go plow  
2 through this with the help of maybe some epidemiologists or  
3 clinical epidemiologists and statisticians, and really take  
4 a good look and see what is happening, because I think we  
5 are past the point of a large Phase III study. It is just  
6 not going to happen.

7 DR. HARMS: I would agree. What we are really  
8 looking at is a palliative treatment. This is a treatment  
9 for liver metastases, so the endpoint is the regression of  
10 liver metastases, it is not survival, because this is a  
11 palliative procedure.

12 So, I think we have got statistical evidence that  
13 that is proven. The big advantage here is the benefit over  
14 the risk, and we are assuming that the denominator is very  
15 small because of the data that we have, that the risk is  
16 very low.

17 I would think if we track anything, we would track  
18 safety over a number of patients, and that can be done  
19 without a randomized trial.

20 DR. TOLEDANO: I had also figured we would be  
21 tracking safety on everybody, so didn't say that explicitly,  
22 just sort of assumed.

23 DR. GARRA: I think at this point, my only other  
24 comment would be that would be the only thing that might  
25 cause people to suddenly shy away from it. They are going

1 to be grab for this one chance and whatever it is. I mean  
2 if it's 50 percent, that's great. People will grab for much  
3 slimmest chances than that if that is their only chance, and  
4 the only things that might dissuade them would be a terribly  
5 high risk of some bad consequence, which we haven't seen  
6 yet, but a little insurance as drugs change might be a good  
7 idea.

8 DR. MALCOLM: I am not sure how to really address  
9 that, that situation which I think we brought up, and that  
10 is how we treat patients in this country versus this study.  
11 I don't know how to say it except again, I think we have  
12 been talking about the safety issues and untoward effects.  
13 I think we have to evaluate those patients and perhaps  
14 compare the new data that has come out with some of these  
15 patients who will be treated with this drug, and watch them  
16 very carefully. I am not sure what else to do at this  
17 point.

18 Question 4. I think this one we just talked  
19 about. Is there a need for mandatory training for users of  
20 the device? If so, please discuss.

21 I think we have discussed this a little bit, and  
22 what the manufacturer said is that they plan, although I  
23 didn't see that directly in the PMA, but that they plan to  
24 have a panel at five different universities of well-trained  
25 individuals.

1 I heard that comment, but I didn't see that  
2 written anyplace. Any comment about that?

3 DR. GRAY: That is correct. We would be very much  
4 of the view that there ought to be mandatory training for  
5 all users.

6 MR. AYRES: If everybody is in agreement, it ought  
7 to be part of the labeling, I would think, the mandatory  
8 part.

9 DR. MALCOLM: Any comment about that?

10 DR. MEHTA: I actually have an NRC-related  
11 comment. Does an interventional radiologist need training  
12 in radiation oncology, does a radiation oncologist need  
13 training in interventional radiology, or do the two need to  
14 work together to do this?

15 MR. AYRES: I would assume we have another team  
16 situation here.

17 DR. GARRA: I think that is, I mean when we are  
18 performing that in our practice. I will position the tube  
19 and then I let the radiation oncologist take over.

20 DR. MALCOLM: We stand in front. We hold the  
21 material. I put the tube in, and they walk out of the room.  
22 See, that is what it is.

23 Any additional comments on No. 4, although I think  
24 we have discussed this one already.

25 I will turn it back over to the chairman.

1 DR. GARRA: Now, I am going it up to members of  
2 the panel for any final comments of discussion points they  
3 would like to make.

4 [No response.]

5 DR. GARRA: I think we have been talking enough,  
6 so everybody is yakked out.

7 So, what we are going to do, we are going to go  
8 ahead and open now the meeting up to the public.

9 **Open Public Hearing**

10 DR. GARRA: Are there any people who wish to speak  
11 that are in the audience?

12 [No response.]

13 DR. GARRA: Seeing none, we are going to close the  
14 public comment section and move on to the panel  
15 recommendations and vote.

16 **Panel Recommendations and Vote**

17 DR. GARRA: First of all, are there any new issues  
18 that the FDA would like addressed that we have not covered  
19 as a panel or that you would like to bring to our attention  
20 at this point?

21 DR. SCHULTZ: I see a lot of head shaking no. You  
22 have done a nice job.

23 DR. GARRA: Finally, there is my question to the  
24 manufacturer. Do you think there are issues that we have  
25 not covered that we should address or that you would like to

1 address before we do our voting?

2 DR. GRAY: No, we don't. We think the panel has  
3 been very comprehensive in its cover, and we take onboard  
4 all of the comments.

5 DR. GARRA: So, we are ready to move on to the  
6 panel recommendations concerning this PMA, P990065.

7 The Medical Device Amendments to the Federal Food,  
8 Drug, and Cosmetic Act, as amended by the Safe Medical  
9 Devices Act of 1990, allow the Food and Drug Administration  
10 to obtain a recommendation from an expert advisory panel on  
11 designated medical device pre-market approval applications,  
12 PMAs, that are filed with the Agency.

13 The PMA must stand on its own merit and your  
14 recommendation must be supported by safety and effectiveness  
15 data in the application or by applicable publicly available  
16 information.

17 Safety, as defined in the Act, is a reasonable  
18 assurance based on valid scientific evidence that the  
19 probable benefits to health under the conditions of intended  
20 use outweigh any probable risks.

21 Effectiveness is defined as reasonable assurance  
22 that in a significant portion of the population, the use of  
23 the device for its intended uses and conditions of use will  
24 provide clinically significant results.

25 As we discussed in the training session this

1 morning, the options for vote are as follows:

2           We can vote that it is approvable without any  
3 conditions, or it is approvable with conditions. In this  
4 case, the panel may recommend that the PMA be found  
5 approvable subject to specified conditions, such as  
6 physician or patient education, labeling changes, further  
7 analysis of existing data.

8           Prior to voting, all the conditions, we should  
9 discuss them.

10           Finally, we can vote that it is not approvable.  
11 The panel may recommend that it is not approvable if the  
12 data do not provide a reasonable assurance that the device  
13 is safe or that reasonable assurance is not given that the  
14 device is effective.

15           At this point, the Chair of the panel will  
16 entertain a motion from a member of the panel regarding  
17 approval, disapproval, or approval with conditions.

18           Dr. Malcolm, as the lead reviewer.

19           DR. MALCOLM: I move that this PMA be approved,  
20 however, I have some conditions on that approval.

21           One is that we assure that the labeling issues are  
22 resolved, that is, the labeling issues from the Regulatory  
23 Commission in regards to safety for the users; that the  
24 labeling issues in regards to some dosimetry is also within  
25 the documentation; and that the education is assured as has

1 been outlined for those users; and patient risk and the  
2 improvement on the risks in patient information consent form  
3 is modified or improved.

4 Those are the three I have in mind.

5 So, I vote for approval with the conditions.

6 DR. TOLEDANO: I will second the motion to approve  
7 with conditions.

8 DR. GARRA: All those in favor of approval with  
9 conditions, raise their hands.

10 [Show of hands.]

11 MR. DOYLE: We have 5 out of 5 have voted in favor  
12 of approval with conditions.

13 DR. MALCOLM: The first condition was labeling.  
14 Any discussion on that?

15 DR. GARRA: State succinctly what you would like  
16 to say.

17 DR. MALCOLM: Improve the labeling to indicate the  
18 conditions of dosimetry information.

19 MR. DOYLE: That is one condition, right?

20 DR. MALCOLM: Right, that is one.

21 DR. GARRA: No, no. The labeling is all one  
22 condition.

23 MR. DOYLE: Improve dosimetry information.

24 MR. AYRES: The exposure rates for personnel  
25 protection.

1 DR. GARRA: That is dosimetry, right?

2 MR. AYRES: No, the other one was actual  
3 dosimetry, patient dosimetry for accurately prescribing the  
4 material.

5 DR. MALCOLM: And the other is handling issues.  
6 We are saying one was the labeling of dosimetry.  
7 The other was in regards to handling the material.

8 DR. GARRA: Radiation protection information.

9 DR. MALCOLM: Radiation protection information.

10 DR. HARMS: Provide radiation protection  
11 information in the labeling.

12 DR. MALCOLM: Specify training for users.

13 I am not sure if this goes in the labeling or not,  
14 I am not sure where to put it. That is patient information  
15 in regards to consent. Is that under labeling? Consent,  
16 because the consent form we have now is clearly not  
17 adequate.

18 MR. AYRES: I am puzzled. When we go to an  
19 approved PMA product, we are no longer dealing with patient  
20 consent, it is just patient information, isn't it?

21 DR. MALCOLM: Okay.

22 MR. DOYLE: Improve patient information.

23 DR. GARRA: Is that clear enough for the FDA to  
24 know what we mean by that?

25 DR. SCHULTZ: Yes, we know what you mean.

1 DR. PHILLIPS: It is typically for patient  
2 labeling.

3 DR. MALCOLM: So, it is all under labeling.

4 MR. DOYLE: The labeling is improve patient  
5 dosimetry information, provide radiation protection  
6 information, specify training for users and improved patient  
7 information (labeling).

8 DR. GARRA: Should we say specify mandatory  
9 training? I don't know. People wanted mandatory in there,  
10 I don't know that you can make it mandatory.

11 DR. HARMS: Isn't that the NRC that does the  
12 mandatory for the user?

13 DR. GARRA: Just specify it and let the NRC  
14 decide.

15 DR. PHILLIPS: In our conditions of approval, one  
16 of the conditions can be that labeling be provided that is  
17 appropriate for training, that training be provided by the  
18 manufacturer for users, and that is one of the conditions or  
19 approval.

20 DR. MALCOLM: We have that in there.

21 DR. MEHTA: The only clarification I have is we  
22 use the phrase "improved dosimetry." My understanding is  
23 that what we were talking about is that there isn't  
24 information regarding dosimetry, so it is really not  
25 improved dosimetry, it is just information regarding

1 dosimetry.

2 MR. AYRES: Information necessary to do proper  
3 dosimetry.

4 Just a question. On the patient information,  
5 looking at the panel pack, page 1800, it isn't clear to me  
6 where the patient information ends. Does it include how the  
7 spheres are used and why they are used?

8 It looks like that would be relevant patient  
9 information, and then you would have several pages on the  
10 place of SIR-Spheres and the treatment. If all that was  
11 part of the patient information, it isn't clear where the  
12 cut-off is intended in here, for what is and what isn't  
13 patient information.

14 DR. TOLEDANO: I believe it goes to page 1807.

15 MR. AYRES: That is quite a bit if it's all of  
16 that.

17 DR. TOLEDANO: It doesn't list the adverse  
18 reactions in the type of detail that we are accustomed to in  
19 clinical trials in this country.

20 DR. GARRA: Given this requirement, the FDA has  
21 people that that is all they do, and they will listen to  
22 this transcript and they will say, oh, this is what we have  
23 got to make sure they had, and I am sure it will be covered.

24 DR. MEHTA: Can you read that back?

25 MR. DOYLE: I only changed one word, but it is the

1 labeling. This all pertains to labeling.

2 Provide patient dosimetry information, provide  
3 radiation protection information, specify training for  
4 users, and improve patient information.

5 DR. GARRA: Those are very general. You have to  
6 realize they will be very specific by the time they are  
7 massaged.

8 DR. SCHULTZ: Were there any comments on  
9 indications, warnings, and precautions? I know you had  
10 discussed it earlier. Were there any specific comments that  
11 you wanted to make on either the general indication  
12 statement or warnings or precautions? No, okay.

13 DR. MALCOLM: I think it was pretty  
14 straightforward.

15 DR. MEHTA: Does it go in the same one?

16 DR. GARRA: That would probably be a separate one.  
17 We could put it in the same one. You could put it in here  
18 now, if you have a comment, go ahead and make it.

19 DR. MEHTA: I think the comment we should make is  
20 specific to the safety information for systemic  
21 chemotherapy, that that needs to be collected for a period  
22 of time in the labeling, because we don't have that with  
23 systemic chemotherapy. There should be some period of time  
24 or some number of patients for which that data is collected.

25 DR. GARRA: That won't go in the labeling.

1 DR. HARMS: I think what Dan is aiming at is the  
2 ascites comment. Do we want to strike ascites out?

3 DR. GARRA: That was the only question.

4 DR. HARMS: Do we need to make a recommendation of  
5 that in this?

6 DR. SCHULTZ: You don't necessarily need to.  
7 Whatever comments you have that you think would be helpful,  
8 anything specifically regarding the way the indication  
9 statement is currently configured.

10 Right now I think the indication is fairly general  
11 in terms of all types of tumors. There was a discussion on  
12 that, that you had earlier. The warnings and precautions,  
13 if there are any specific recommendations that you have in  
14 terms of reconfiguring or making those more specific, that  
15 would be helpful. If not, then, we will go back and re-read  
16 the transcript and try to do the best that we can to try to  
17 discern some of the comments that were made earlier.

18 DR. HARMS: In that regard, I don't think I would  
19 modify the conditions.

20 DR. GARRA: So, their original intended use was--  
21 and this is what I would say in the labeling--liver tumors  
22 of primary or secondary origin, that are not suitable for  
23 resection. Do we want to be a little more specific than  
24 that? It is not going to affect the actual usage  
25 necessarily. It just will keep it within the bounds of what

1 they have demonstrated to the panel.

2 DR. MALCOLM: What I heard today, and what I have  
3 discerned from the PMA, is all on metastatic disease, not  
4 primary disease.

5 DR. TOLEDANO: But the sponsor has noted that in  
6 their original PMA submission that went to the FDA, they  
7 have included data on primary HCC, and I think we have to  
8 leave that up to the FDA. That is just my personal opinion.

9 DR. HARMS: I agree.

10 DR. GARRA: I thought there was some data. It was  
11 a small amount. So, the way I see it, there is a couple of  
12 options. We could say leave it the way it is, we could say  
13 primary liver cancer and colorectal cancer, or we could say  
14 just colorectal cancer, increasing levels of restriction.

15 DR. TOLEDANO: I have a compromise. My compromise  
16 is that since the panel received only the panel pack of some  
17 of the data, and the FDA received the entirety of the data,  
18 that we should urge the FDA staff to appropriately consider  
19 the indications.

20 Would that be a reasonable compromise?

21 DR. GARRA: What was your compromise again?

22 DR. TOLEDANO: Have the FDA staff, based on the  
23 entirety of the data, carefully consider the complete  
24 indications.

25 DR. GARRA: I think they are asking us for some

1 guidance on that, though. That is why they put that  
2 question in there.

3 DR. MEHTA: I would say that if we, as a panel,  
4 have to make a recommendation on the data that we have seen,  
5 we have seen very narrow data, and they are in colorectal  
6 cancer metastasis, and patients with no extrahepatic  
7 metastasis, we may expand that to say colorectal cancer in  
8 any patient, so extrahepatic metastases are permitted. We  
9 may expand that to say metastasis from the GI tract. We may  
10 expand that to say metastasis from any origin.

11 We might expand that to say metastasis in primary.  
12 But at some point we need to have a data-driven decision,  
13 and the data we have seen are colorectal cancer metastasis.

14 DR. GARRA: Let's vote on this one, and then put a  
15 separate statement in a recommendation to the FDA regarding  
16 what we think the indications ought to be, and let them  
17 decide. I don't want to tie up all these other ones with  
18 this other one that is proving to be a little bit complex.

19 Let's just finish the vote on this first labeling  
20 section. It doesn't include the indications, but the other  
21 four items that were mentioned.

22 All those in favor, raise your hands.

23 [Show of hands.]

24 DR. GARRA: So, there is 5 yes's.

25 MR. DOYLE: And that's all there are, 5 of 5.

1 Five of 5 voted in favor of that condition.

2 DR. GARRA: Now, regarding labeling with respect  
3 to indications. We can leave it up to the FDA or we can be  
4 very specific. We can go in several different directions  
5 here.

6 DR. MEHTA: Isn't it common practice that as more  
7 data develop and evolve for other indications, that the  
8 label is changed?

9 DR. GARRA: Is that done administratively at the  
10 FDA or how is that done?

11 DR. PHILLIPS: By supplement.

12 DR. HARMS: I agree with Dr. Mehta. I feel  
13 uncomfortable approving something I don't have data to  
14 support.

15 DR. GARRA: We have got to draw the line  
16 somewhere. If we don't have any data whatsoever, I think we  
17 really have to be specific, and it won't necessarily  
18 restrict people from using it off-label.

19 DR. MALCOLM: I think from the information we  
20 have, the only indication we have at this point is  
21 metastatic colorectal cancer. That is the data I reviewed.  
22 That is what I have, I don't have anything else.

23 It may be expanded beyond that at some point, but  
24 I can only vote on what I had a chance to review.

25 DR. GARRA: So, would you like to make a motion?

1 DR. MALCOLM: I make a motion that the indications  
2 for the use of this device be for metastatic colorectal  
3 carcinoma.

4 DR. MEHTA: Second.

5 DR. GARRA: Any discussion?

6 Okay. Those in favor, raise your hands?

7 [Show of hands.]

8 MR. DOYLE: We have four.

9 DR. GARRA: Those opposed?

10 [No response.]

11 MR. DOYLE: One abstain?

12 [1 hand raised.]

13 MR. DOYLE: We have 4, 4, and 1 abstained.

14 DR. GARRA: I think we should make a comment in  
15 this, and this will go in the record, that we feel it is  
16 likely it will be helpful in other areas, just we simply  
17 were not presented the data at this point to make that  
18 decision.

19 DR. MALCOLM: Clearly, what it comes down to is I  
20 can only vote on what I have, and it does appear--in fact, I  
21 see no reason why it could not work in other diseases  
22 besides colorectal. We chose that area, but as we know,  
23 there are multiple other tumor sites that go to liver  
24 metastasis.

25 DR. GARRA: Given the difficulties of patient

1 accrual, getting enough to submit for another less common  
2 metastatic process would have been almost impossible. We  
3 recognize the difficulties that the manufacturer had, and we  
4 expect that as this comes on line, it will be used  
5 elsewhere.

6 MR. DOYLE: The indication for use, the device be  
7 used for metastatic colorectal liver cancer.

8 DR. GARRA: Can I--we voted on that, it is too  
9 late to amend it--I was thinking of amending the amendment.

10 DR. HARMS: It should be unresectable, but  
11 presumably you are just adding this to the unresectable  
12 part.

13 DR. GARRA: Yes.

14 DR. HARMS: And we are going to way without known  
15 metastases, weren't we?

16 DR. GARRA: I don't think the data they presented  
17 to us, they had other metastases. I think that would be  
18 going too far.

19 The only other comment I would make for the  
20 record, for the FDA, is that if the FDA comes into its  
21 possession, other information regarding primary  
22 hepatocellular carcinoma that did not appear in our booklet,  
23 that they move aggressively towards approving it for that.  
24 I think the panel would agree with that.

25 MR. DOYLE: So, we have two conditions. Are there

1 any more conditions?

2 DR. TOLEDANO: I will do the next one.

3 I move that we mandate post-market studies of the  
4 safety and efficacy of the SIR-Spheres, safety monitoring of  
5 all patients, and in the efficacy study, that would be an  
6 observational study collecting endpoints and patient  
7 information. Actually, let's just do it this way.

8 I move that we mandate post-market studies--post-  
9 approval studies of safety and efficacy and effectiveness to  
10 be designed with the FDA.

11 MR. DOYLE: Do you want to cover some specific  
12 topics?

13 DR. TOLEDANO: Yes, that they would be  
14 observational, just that we recognize that this would be an  
15 observational study.

16 DR. GARRA: I would like to maybe suggest that  
17 they include use of the agent with systemic chemotherapy,  
18 the use of systemic chemotherapy agents.

19 DR. MEHTA: I just have a question of  
20 clarification on that.

21 I like the idea of building this in. Do we  
22 necessarily want to box ourselves into an observational  
23 study, because there are precedents with other things, and I  
24 know we are not supposed to talk about other things, so I  
25 won't name them, where observational studies have been done

1 post-market and in certain instances, even Phase III  
2 randomized trials have been done post-market.

3 So, I am not sure that we should close any doors.  
4 I think if we say it is going to be done in consultation  
5 with the FDA, maybe we should leave it that way.

6 DR. TOLEDANO: Maybe we should say that an  
7 observational study would be acceptable, if that is okay,  
8 because I also don't want to box into a Phase III, which I  
9 don't think there is any possibility of doing.

10 Let's see how much Bob has written. It looks like  
11 half a page already. I would like Bob to read it.

12 MR. DOYLE: Mandate post-approval study of safety  
13 and effectiveness to be designed with the FDA (an  
14 observational study is acceptable), and then including use  
15 of the device with new systemic chemotherapy agents.

16 DR. HARMS: Second.

17 DR. GARRA: Any further discussion on this?

18 All those in favor, raise your hands.

19 [Show of hands.]

20 DR. GARRA: So, 5 out of 5.

21 MR. DOYLE: For the recording, it is 5 in favor.

22 DR. GARRA: Are there any further conditions?

23 MR. AYRES: I would just like to mention something  
24 maybe for the FDA, not necessarily a condition unless the  
25 rest of the panel thought so, I thought under

1    contraindications and precautions, the restrictions on  
2    pregnancy were a little tight, and not in accordance with  
3    common medical practice.  In other words, they are saying it  
4    is contraindication to use this treatment for pregnant  
5    women, and down in precautions, they say you should  
6    establish non-pregnancy.

7                    I would assume in the case of metastatic liver  
8    disease in particular, the issue is really determining  
9    pregnancy, and then it is a decision between the woman and  
10   her physician, whether pregnant or not, whether the  
11   treatment is appropriate, because pregnancy may be the  
12   secondary issue in this kind of disease.

13                   I just was commenting on I thought that the  
14   contraindications and precautions were a little restrictive.  
15   One last comment on the warnings.  On the patient's exposure  
16   to members of the public is already covered by our patient  
17   release rule, which establishes mandatory requirements  
18   there, so it may be a bit redundant.  It doesn't hurt  
19   anything being in there.

20                   DR. GARRA:  So, we have those comments, and the  
21   FDA can look at those and take those under advisement.

22                   DR. MEHTA:  Can I ask for a clarification on that  
23   comment?

24                   DR. GARRA:  Yes.

25                   DR. MEHTA:  Do I understand you correctly in

1 saying that the NRC would be okay with a pregnant patient  
2 receiving an injection of yttrium microspheres?

3 MR. AYRES: As long as the physician knows the  
4 patient is pregnant, and the decision is made that it is in  
5 the best interest of the patients to proceed.

6 What we have a problem with is inadvertent  
7 administration of byproduct material to patients who are  
8 pregnant, but the physician didn't know it. When it is done  
9 with medically informed administration, we have no problem.  
10 That is the practice of medicine.

11 Making a mistake in administering material to a  
12 pregnant or a breast-feeding woman, that is where we have a  
13 problem.

14 DR. GARRA: I think the FDA folks can look at this  
15 issue and decide, you know, with other similar--well, they  
16 don't have similar agents--but they have other situations  
17 where this has arisen, and decide what might be best. The  
18 manufacturer obviously thought it was a reasonable way to  
19 go, to put that in. Is that true? You weren't coerced into  
20 putting that in or anything, were you? Okay.

21 I mean the legal issues of exposing the fetus if  
22 there were a mishap--

23 MR. AYRES: I mainly brought it up because there  
24 is probably some instances where the patient wouldn't be  
25 expected to survive until term anyway. I wanted to make it

1 clear that we do not have a blanket prohibition against  
2 administering radioactive material to pregnant women.

3 DR. GARRA: Thank you. That is useful. I think  
4 the lawyers may have already created one for us.

5 Do we have to address the education issue again,  
6 Alicia, do you think so? We have training in the labeling.  
7 It just describes it. Did we specify that it has to be  
8 mandatory there? I don't think so.

9 DR. TOLEDANO: It will be. Delivery.

10 DR. MALCOLM: There was a question about delivery.  
11 She is correct, there was a question about delivery, that  
12 they were saying in Asia they do it one way, in Australia  
13 they do it another way, and we were saying it was up to the  
14 individual physician, correct, isn't that what was said?

15 DR. GARRA: They would have to supply that  
16 mechanism for delivery, but the physician would still be  
17 able to use whatever they wanted. I think that is the way  
18 we want it.

19 MR. MONAHAN: They would have to make the  
20 administration set available.

21 MR. AYRES: And if it is part of the PMA, the firm  
22 has a process of going through and getting this approved by  
23 us, which they haven't started, and it could end up becoming  
24 a mandatory way of administration, although I understand in  
25 both our case and in FDA's, they could probably add the

1 syringe method by supplement. Would that be correct?

2 DR. GARRA: It sounds to me like it's a good  
3 method. It sounds to me like we may be arguing over sort of  
4 a non-issue.

5 MR. AYRES: I think what would be important would  
6 be to get the data on the relative exposures to individuals  
7 using either method and whether one is better or they are  
8 equal.

9 DR. GARRA: But that is something you will  
10 certainly address, I am sure.

11 I believe that that is all the conditions that we  
12 have to place, so now we have a blanket vote on the approval  
13 with all the listed conditions that we have all individually  
14 approved.

15 Those in favor of recommending approval of this  
16 device with the conditions, raise your hands.

17 [Show of hands.]

18 DR. GARRA: That is 5 out of 5.

19 One more time I will clarify that the motion was  
20 for approval with conditions, recommendation of approval  
21 with conditions.

22 That is where we stand right now. Before we  
23 adjourn for the day, I would like to remind the panel  
24 members that they are required to return all the materials  
25 they were sent pertaining to the PMA. The materials you

1 have with you may be left at your table, any others may be  
2 sent back to the FDA as soon as possible.

3 I wish to thank the speakers and members of the  
4 panel for their preparation, and we have one more comment.

5 DR. SCHULTZ: Just one more request,  
6 administrative request is that you need to go around one  
7 time and have everybody give a brief description as to why  
8 they voted the way they did.

9 DR. GARRA: Yes. As we go around the table, each  
10 person will give just a brief summary of why they voted the  
11 way they did, and strictly speaking, it's panel members, but  
12 we would like to hear from the industry representative, as  
13 well, and other non-voting reps.

14 DR. MALCOLM: I voted to approve this device  
15 because I think that although the information has been  
16 limited, I think it appears that it is safe; two, that it is  
17 potentially another arm or weapon that we have against this  
18 particular situation, the patient with hepatic metastases,  
19 and I think that perhaps in the future, we will start to  
20 make some inroads in these patients who perhaps in these  
21 cases may not continue to be palliative cases, but we may  
22 actually cure some of these patients with reduction of  
23 disease and then followed by resection.

24 I again stand on my vote of approval for this  
25 device.

1 DR. TOLEDANO: I voted to approve with conditions  
2 because I see a lot of great hope and a lot of solid work,  
3 and the reason I put conditions on it was that I see more  
4 information that needs to be gained before I would feel  
5 completely comfortable with the safety and effectiveness in  
6 current practice today in this country, but I think there is  
7 a lot of hope.

8 DR. HARMS: I agreed to support approval with  
9 conditions because this should be a great treatment for a  
10 number of patients that have very little choice right now,  
11 and I think the number of indications will probably grow  
12 over the years.

13 DR. MEHTA: I also voted to approve with  
14 conditions for two main reasons. First, I believe that this  
15 brings in a therapy that actually improves the therapeutic  
16 index for patients with widely disseminated liver metastasis  
17 for whom we really don't have a good treatment today.

18 Secondly, I believe that with appropriately done  
19 and better controlled studies, this treatment actually has  
20 the potential to improve survival in selected subsets of  
21 patients, which I would strongly urge the manufacturers to  
22 pursue in the future.

23 DR. IBBOTT: I also voted to recommend approval  
24 with conditions because I believe this treatment should be  
25 made available and because my questions about the safety

1 issues have addressed either by the sponsor or the  
2 recommendations that we have made.

3 MR. AYRES: I would favor approval of this, as the  
4 committee did, because I think the benefit-risk ratio is  
5 favorable in this case.

6 MS. PETERS: I am glad that the panel did approve  
7 it, and I am happy to see that so many of the clinical  
8 people were interested in patient information, that that be  
9 put in.

10 MR. STERN: This is my first meeting, and I was  
11 extremely impressed both by the panel and by the sponsors,  
12 and had I voted, I would have voted with the panel.

13 DR. GARRA: I wish to thank the speakers, members  
14 of the panel for their preparation, and I wish to thank  
15 Arnold Malcolm specifically for leading the discussion  
16 segment of the meeting.

17 I would just like to make a concluding comment  
18 that I think this is going to be a big help for a lot of  
19 patients who are desperate for any kind of hope that can be  
20 given to them.

21 There being no further business, I would like to  
22 adjourn this meeting.

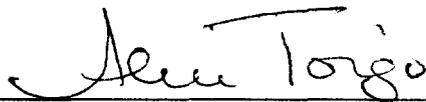
23 [Meeting adjourned at 3:12 p.m.]

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**C E R T I F I C A T E**

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a horizontal line.

**ALICE TOIGO**