

1 other areas, we see additional opportunity
2 for improvement.

3 And let me point out that one of
4 the downsides of speaking about qualitative
5 goals is that these things aren't measured,
6 and we don't have good metrics around them,
7 so much of what I will be sharing with you is
8 anecdotal information.

9 But those of you who deal with
10 things like customer complaints or
11 constituent complaints on a day-to-day basis
12 realize that you can get a pretty good feel
13 for how things are really working based on
14 the amount of background noise around
15 something.

16 I did want to point out, if you
17 look at CDRH's 2006 priorities, you will see
18 that the performance record in fiscal year
19 '05 has been good, and also that there has
20 been focus on more than just the performance.
21 It's been on a change in the culture, and I
22 think this is particularly important to tie

1 in to the qualitative goals; that the
2 coordination of all the activities that lead
3 to the quickest possible time to market for
4 products, and the accountability on both
5 sides, both industry and FDA, is something
6 that we need to pay attention to. And I
7 think we also appreciate the fact that FDA
8 has identified continued improvement as one
9 of their goals.

10 So "Scheduling of Meetings," you
11 have already heard a few words about that in
12 the goals letter that was done at the time of
13 MDUFMA in 2002. FDA and the industry stated
14 that both agreed that the use of informal and
15 formal meetings is critical not just to
16 ensure high application quality, but also to
17 ensure speedy reviews.

18 Yet AdvaMed members are currently
19 indicating that scheduling of meetings is
20 becoming more and more a concern, and I think
21 it goes without saying that improvements in
22 scheduling are going to be important to

1 assure that the overall intent and the
2 specific performance goals are met.

3 So I would encourage us on both
4 sides to try to develop some meaningful
5 metrics around scheduling of meetings, how
6 long does it actually take to get meetings
7 scheduled, and how does that play into the
8 full review cycle?

9 PMA Modular Reviews. The Industry
10 has always been very supportive of modular
11 review. It has a lot of benefits in that as
12 you finish up a particular area,
13 pre-clinical studies, for example, you can go
14 ahead and put the submission in, get
15 questions on the table, get those questions
16 answered, and optimistically not have to go
17 back and re-review that.

18 It also provides an opportunity for
19 FDA to get some of the work done ahead of
20 time and really to be able to focus on the
21 clinical data as the last piece of
22 information that goes into the review cycle.

1 FDA's perspective on modular PMAs has been
2 mixed, some people seem to favor them, other
3 people are concerned about the additional
4 resources that are required, but certainly
5 from an industry perspective, we would
6 encourage you to continue this program. And
7 more importantly, we think there should be
8 specific performance goals for modular PMAs,
9 and would be interested in seeing this as an
10 element for MDUFMA reauthorization.

11 And in terms of setting metrics for
12 that module should be closed and in a timely
13 fashion, and in order to do so, questions
14 would have to come back from FDA to the
15 company in a very timely fashion, and we are
16 suggesting that 75 days for questions, and 90
17 days to review a completed module, should be
18 appropriate.

19 I don't believe that we talked
20 about bundling last year, but bundling was a
21 real concern that the industry brought up
22 back again in 2002. On both the device and

1 the diagnostic side, there were concerns that
2 FDA would try to find a way to split a
3 product or a product line into too many
4 separate applications in order to collect the
5 fee. And in reality, that's not what has
6 happened.

7 On the medical device side,
8 bundling, I think, has been very effective.
9 On the in-vitro diagnostic side, it may
10 require some reconsideration. FDA did put
11 out a guidance on bundling. A specific
12 example provided by one AdvaMed member is
13 that that guidance specifies that for
14 anti-microbial susceptibility tests, one
15 submission is required per drug, and can
16 cover both gram positive and gram negative
17 organisms.

18 In fact, that has not always been
19 the case, the actual decision is made on a
20 case-by-case basis, and the result of this is
21 that the fees for some in-vitro diagnostic
22 products are disproportionately large. Just

1 to provide one example for one particular
2 product platform, 56 submissions were
3 required that actually covered only 22
4 products. So in that case, the effective
5 510(k) fee was \$8000 per product.

6 And ending on a positive note, last
7 year, we mentioned the need for coordination
8 in the timing of pre-approval inspections,
9 because various AdvaMed members were noting
10 that these were holding up the final PMA
11 approval. And we also noted that this was
12 not only responsibility on the part of FDA,
13 but also that it was important for sponsors
14 of PMAs to be sure that this was incorporated
15 in their project planning, and that in fact
16 they would be prepared for their pre-approval
17 inspections at the appropriate time.

18 The good news this year is that the
19 noise level around this issue seems to have
20 gone down substantially, indicating that in
21 more and more instances, FDA is able to
22 appropriately schedule the pre-approval

1 inspections so that they don't in fact hold
2 up the final decision.

3 So in summary, what I'd like to say
4 is that we have certainly seen some
5 significant areas of improvement in
6 qualitative goals. There are still some
7 opportunities that remain in a variety of
8 areas. I think both FDA and the industry
9 agree that these are important, and these are
10 areas in which we should try to establish
11 some baseline metrics, and wherever possible,
12 some goals for a MDUFMA reauthorization.

13 Thank you.

14 MR. BARNETT: Thank you, Pat. Is
15 there anyone on the panel who wants
16 clarification. Yes, Joanne?

17 MS. LESS: Pat, sorry, I don't have
18 much of a voice. One of the previous
19 speakers mentioned the difficulty in
20 scheduling pre-IDE meetings.

21 MS. SHRADER: Yes.

22 MS. LESS: And in your slide, you

1 just referred to meetings in general, so are
2 you seeing it across all the three program
3 areas, or still predominately in IDE area?

4 MS. SHRADER: I think it crosses
5 this all three program areas. My own
6 experience has been with informal meetings,
7 and scheduling is becoming difficult.

8 MS. LESS: Okay, thank you.

9 MR. BARNETT: Tim?

10 MR. ULATOWSKI: Yes, Pat, perhaps
11 you want to respond, or it may generate other
12 responses after you, because I think you are
13 the only scheduled speaker, but anyway, a
14 couple of things: What are your views in
15 regard to pre-IDE meetings and IDE meetings,
16 participation of compliance folk to discuss
17 GMPs and BIMO aspects during the course of
18 the early days of investigations?

19 MS. SHRADER: Well, I think
20 certainly getting input on any expectations
21 around inspections, whether they be BIMO or
22 GMP inspections, is important. So I think

1 that having participants from FDA who can
2 address those areas and give some insight
3 into what they maybe looking for and what
4 their concerns might be would be appropriate.

5 MR. ULATOWSKI: You mentioned the
6 "not ready for inspection" aspect.

7 MS. SHRADER: Yes.

8 MR. ULATOWSKI: What has the
9 industry done, to your knowledge, to make
10 improvements in regard to this aspect?

11 MS. SHRADER: Well, I think that
12 the trade associations have certainly carried
13 the message home to all of their members that
14 this is a collaborative effort, and for
15 industry to make this process work as well as
16 it should, that it's very important that we
17 be very mindful of timing and scheduling, be
18 mindful of the workload that FDA has and make
19 sure that we are in there prepared and
20 talking to the appropriate people at the
21 appropriate time. So I think the
22 associations have done a good job of letting

1 their members know.

2 MR. ULATOWSKI: Let me just ask a
3 third question: People are keeping track of
4 my questions here. What are your views
5 regarding what I will call early intervention
6 inspections; for example, on BIMO, as a means
7 to reduce total process time for PMAs?

8 MS. SHRADER: I'm not clear what
9 you mean by "early intervention."

10 MR. ULATOWSKI: Meaning inspections
11 during the early course of investigations to
12 perhaps reduce the back-end load on the BIMO
13 inspections, when things are coming to a head
14 at the end.

15 MS. SHRADER: Well, I would have to
16 give that a little additional thought. One
17 concern that I would express is that I don't
18 think that the BIMO inspections can be
19 terribly early in the process, because
20 experience with clinical investigation
21 suggests that you select your investigators,
22 get all your agreements in place, you go in

1 and train the investigators.

2 But depending on the device, there
3 may be a learning curve, and as a result,
4 companies do try to monitor their studies
5 carefully, and in fact, may intervene early
6 themselves to try to either make changes in
7 techniques, changes in devices, or changes in
8 training for investigators. So I think
9 earlier rather than later is a positive, but
10 I would caution against trying to get
11 involved too early in the course of a
12 clinical investigation.

13 MR. ULATOWSKI: Thank you.

14 MR. BARNETT: Anyone else on the
15 panel who wants to add anything? How about
16 in the audience? Yes, we have a lot of them,
17 okay.

18 MS. VALENTI: To the last point, I
19 would reiterate what Pat indicated in regards
20 to the clinicals: That we do have to
21 intervene early on in the process sometimes
22 in order to correct those. So I think it is

1 more appropriate for the sponsor to do that
2 rather than using the resources of FDA to do
3 that.

4 So moving it not necessarily at the
5 end, but closer to the end would probably be
6 more appropriate. But your question in
7 regards to having the Office of Compliance at
8 the meetings early upfront during the IDE
9 process I think is very critical, especially
10 for combination products. And where we are
11 looking at which of the GMPs and QSR should
12 apply for that product, I think in that case,
13 it would be very critical.

14 MR. BARNETT: Thank you. Before we
15 go to the next one, let me ask our
16 transcriber, if someone has spoken before, is
17 it still necessary to identify themselves?
18 Where are you, transcriber?

19 COURT REPORTER: No, unless I can't
20 remember their names.

21 MR. BARNETT: So it's only when
22 they haven't spoken before. Thank you. All

1 right, who is next?

2 MR. DURGIN: Bob Durgin with
3 Biomet. I just want to speak about one of
4 the things that I think we have seen work
5 well from our experience, and that is the
6 Office of Compliance's review of
7 manufacturing modules of PMAs. I want to
8 compliment the Office of Compliance for their
9 internal metrics.

10 I know there are no performance
11 goals in this area, but we have seen very
12 good performance on those internal metrics.
13 There has been good accessibility of the
14 staff, informal discussions during the review
15 process. And we have also seen very timely
16 scheduling of a pre-PMA inspection.

17 I guess the one area where I think
18 there is still some room for improvement is
19 similar to what we see in the other
20 performance goals, that there be focus on the
21 total decision time as opposed to meeting
22 just the individual cycles for reviews.

1 I think we have seen in one of our
2 PMAs a number of letters where the
3 internal -- I think it's 30-day goal -- has
4 been met, but ultimately there were more
5 cycles than I think was necessary in the
6 process. But overall, I think it really has
7 been an area that's worked well and there has
8 been significant improvement.

9 MR. BARNETT: Thank you. Anyone
10 else? We had several hands earlier. Please?

11 MR. LASERSOHN: First of all, I
12 apologize for stepping up here each time. I
13 didn't realize that we could present at the
14 end of each session, so I going to do it this
15 way. First, a caution, as I said before:
16 Trying to apply quantitative metrics to
17 qualitative performance goals is very
18 problematic, and the natural tendency is
19 always to measure something -- it would not
20 matter what it is -- whether that is really,
21 what matters or not.

22 And for those of you who do

1 clinical trials, you know that that's always
2 a problem, measuring things, or you tend to
3 measure what you want to measure or what's
4 easy to measure, and sometimes the stuff
5 that's much more difficult to measure is the
6 stuff that really matters.

7 So I will get to that point in a
8 second. But speaking of quantitative goals
9 with respect to qualitative, as the last
10 speaker indicated, the total cycle time for
11 regulatory approval is what matters to our
12 members.

13 And clearly one of the things that
14 we can do is begin to measure that, so that
15 instead of thinking about merely the cycle at
16 the end of a four- or five-year approval
17 process, we really need to start to keep
18 track of the total time for an approval of a
19 product, starting from the very first
20 communication, for example, by a sponsor with
21 the FDA with respect to a particular
22 approval. We have to begin to measure that.

1 And I think that we would find that beginning
2 to focus on that, just to at least measure
3 it, would be very, very productive.

4 With respect to the qualitative
5 types of improvements that we can make for
6 qualitative outcomes, I think we have to look
7 at broader regulatory changes rather than
8 trying to quantify performance measurements.
9 So for example, we will be proposing in this
10 next cycle that the entire risk-based
11 assessment process be given much much greater
12 priority, and that a risk-based approval
13 process really be defined as a separate
14 process.

15 A sponsor should be able to put
16 things to request that approval cycles be in
17 a different category, even if they are PMA or
18 510(k) or de novo 510(k), that we can create
19 a new category, a new pathway on a risk-based
20 basis.

21 Similarly, we believe that it's
22 necessary to begin to think about a separate

1 process for novel devices. That is, if one
2 of our companies walks in with something that
3 we know you have never seen before, it really
4 makes no sense to attempt to fit it in into
5 an existing PMA or 510(k) process, and there
6 should be a mechanism for requesting -- not
7 an expedited process; that's not at all what
8 we are talking about, but a process that
9 recognizes the novelty of a particular
10 device, and as a result, is going to bring
11 different resources of the FDA to bear and
12 make additional resources of the FDA
13 available to avoid the problem of negotiating
14 endpoints for a year or two in an IDE trial
15 because the reviewer has simply never seen
16 such a thing before and is going through a
17 long learning curve.

18 So we are going to be emphasizing
19 qualitative changes in process, or new
20 qualitative processes in order to address
21 these qualitative performance requirements.

22 MR. BARNETT: Thank you.

1 MR. ULATOWSKI: I have one
2 question.

3 MR. BARNETT: Yes, please.

4 MS. KAHAN: Could you clarify what
5 you mean about that first category of risk
6 based -- I'm sorry, risk-based products --
7 and we usually think of it as risk benefit.
8 Are you talking about qualitative --

9 MR. LASERSOHN: Well, of course,
10 risk benefit is a safety question, and there
11 is an explicit de novo 510(k) process which
12 is a risk-based process, but it technically
13 applies only to products that don't fall into
14 other categories.

15 What we are going to request, for
16 example, is that on products that we believe
17 are demonstrably safe, that we can put them
18 into a different review category and treat
19 them in a different way so that there is an
20 explicit understanding, not so much at the
21 top of CDRH, which frankly we think works
22 very, very well, but at the staff level of

1 CDRH, that they must consider risk
2 adjustments to, for example, the endpoints of
3 clinical trials.

4 This is, I would say, of all of the
5 things that we encounter, the risk-benefit
6 discussion around the question of what kinds
7 of assurance of efficacy do we need, what
8 kinds of evidence do we need, has been one of
9 the most difficult problems we've faced with
10 the FDA in the past five years.

11 That is, there should be an
12 adjustment -- since the statute requires for
13 a reasonable assurance of efficacy -- there
14 should be an adjustment of the efficacy
15 evidence requirements based on the relative
16 safety or lack of safety or risk of the
17 device.

18 And while the top of the CDRH
19 clearly understands that, that is really not
20 understood at the staff levels, so we think a
21 process that would elevate, for example, that
22 aspect of a particular approval would help

1 the staff to apply the correct metrics. So
2 that's the kind of suggestion that we would
3 be making.

4 MR. BARNETT: Someone else up here
5 had a question? It's answered, okay. Anyone
6 else in the audience want to speak? Yes,
7 sir, come on up.

8 MR. TOTAH: Good morning, Alan
9 Totah with Cyberonics. Just one point I
10 think I would like to make to the panel, have
11 you consider: when companies develop not only
12 new, unique technology, but if they are
13 developing new indications that the Center
14 has never had to deal with before, we would
15 ask that where the reviewing branch or
16 division does not have that expertise, and I
17 know we have to separate your jobs a little
18 from our jobs, but in reality most of us in
19 the regulatory profession, we are all doing,
20 roughly, the same thing.

21 If the company has an expertise,
22 which they obviously do since they have gone

1 through a trial to develop the data, we would
2 ask that they should consider meeting with
3 the company if the company is willing, so
4 that we can provide some in-depth knowledge
5 about the new indication, the expertise to
6 help the process of determining safety and
7 effectiveness a quicker process.

8 We often know that within each
9 division, they may not have all the
10 expertise, and they will go to another
11 division to get that expertise, but in some
12 cases that doesn't even exist. And for some
13 unique products or indications, the expertise
14 may reside fundamentally within that company.

15 And I know, speaking for my
16 company, and I'm sure many other companies
17 here, we're very willing to meet with FDA
18 early in the review process to help provide
19 education, answer questions, to help the
20 review process move more quickly. So that's
21 my only comment. Thank you.

22 MR. BARNETT: Thank you, anyone

1 would want to respond to that? Okay, anyone
2 else in the audience? Going, going and gone
3 for lunch.

4 It's time to eat now; you have
5 gotten in your handouts some local places
6 where you can eat. There is also a dining
7 room in the hotel.

8 I have 11:30 a.m., why don't we
9 plan on being back here at 12:30 p.m.

10 Thanks.

11 (Whereupon, at approximately
12 11:30 a.m. a luncheon recess was
13 taken.)

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1 be looking at innovative products that we
2 don't fully understand, whether it be looking
3 at the review process and making sure that
4 we're focusing on what it is that really
5 needs to be done, and whether it be looking
6 at resource issues that clearly, clearly are
7 part and parcel of making sure that we're
8 able to accomplish all of these lofty goals.

9 So I just wanted to say hi, I got
10 to do it on a little tape, but I just wanted
11 to say hi in person and to thank each and
12 every person that came to this meeting, and
13 to tell you that we are certainly looking
14 forward to working with you to try to realize
15 a lot of what you are discussing here today.
16 Thank you very much.

17 MR. BARNETT: Thank you, Dan. And
18 now for our first scheduled speaker for this
19 session, we have a return of Bob Britain from
20 NEMA.

21 MR. BRITAIN: I'm sure you can hear
22 me; I just can't hear myself over this air

1 conditioning unit up here. I think most of
2 you know the original intent for seeking
3 legislation to allow for third-party
4 inspections was to be a win-win situation for
5 both FDA and industry.

6 Now FDA would receive inspection
7 reports of participating manufacturers every
8 two years, whereas at least several years
9 ago, FDA inspection frequency was as high as
10 every six years, so this would have been a
11 big boost to FDA.

12 Manufacturers, on the other hand,
13 would submit to more frequent inspections,
14 with the thought that the FDA inspections
15 could be meshed with EU notified body audits,
16 making the whole process more efficient. We
17 will not know for sure whether this goal is
18 achievable until the process is up and
19 running, which it isn't yet. Since a large
20 number of medical device manufacturers have
21 global businesses, it makes sense to push the
22 third-party inspection concept globally or

1 even regionally.

2 And to do this successfully,
3 however, you need to have a successful track
4 record, and this is where FDA comes in, as
5 many countries with developing programs look
6 to FDA as the gold standard. And this is why
7 it is so important that the third party or
8 accredited persons program works
9 successfully. If it doesn't, we will have
10 much difficulty selling this abroad.

11 A few concerns. There are many
12 issues that need to be addressed and solved
13 before this program will be successful. The
14 process for accrediting accredited persons
15 and their organizations has been slow and
16 arduous and expensive for both FDA and the
17 accredited person organizations. It is
18 simply not simple to qualify auditors or
19 these organizations.

20 Scheduling prequalification audits
21 is difficult. FDA's availability rarely
22 coincides with the manufacturers' audit

1 schedule. So far, only five of fifteen
2 organizations in MDUFMA are accredited to
3 perform inspections. And since it has been
4 several years since MDUFMA was enacted, I
5 don't know how many of the auditors have to
6 be actually retrained. I'm not sure about
7 that.

8 Besides the problems in getting the
9 accredited persons and their organizations in
10 place, the current program is cumbersome and
11 far from user-friendly. Entering the program
12 and staying in the program for manufacturers
13 has yet to be tested. On paper, it has its
14 drawbacks. Having to change accredited
15 persons after so many inspections may be a
16 burden for some manufacturers. These reasons
17 alone may limit the participation by
18 manufacturers in the program.

19 Even if some manufacturers make it
20 through the hoops and hurdles, participation
21 will be small in the beginning. You have to
22 expect that. It took several years to be

1 considered the third -- we saw this with the
2 510(k) third-party review program, because it
3 took several years to be considered a
4 worthwhile program for FDA.

5 The bright side is that many of us
6 in the industry are optimistic about the
7 accredited persons program; we want to make
8 it work. But it will be a matter of trust
9 and willingness on FDA's part to work with
10 the industry to make the program, number one,
11 least burdensome and efficient, and to be
12 done at reasonable cost. And so we have
13 hopes. We need to make it work; we need to
14 take it global. That's the only thing that's
15 going to save this industry from hundreds of
16 inspections. Thank you.

17 MR. BARNETT: Thank you, Bob.
18 Anyone on the panel want to respond to that?

19 MR. NIEDELMAN: The only thing I
20 would like to just suggest, and Bob knows
21 some of this: We do have five accredited
22 persons that are currently available, and

1 those who are Class II and III manufacturers
2 should shortly be receiving a letter that I
3 just signed a few days ago indicating that
4 these five are available, but there is new
5 guidance out there since the middle of
6 September on how to use the AP Program. And
7 we certainly encourage firms to offer their
8 facilities as audit sites so we can get more
9 of these APs through the system as rapidly as
10 possible. It is not easy, as Bob said, to
11 schedule a lot of these audits.

12 MR. BARNETT: Thank you, Steve.
13 Anyone in the audience want to respond?
14 Let's go to our next speaker, Diane
15 Wurzburger, from AdvaMed.

16 MS. WURZBURGER: Good afternoon.
17 Diane Wurzburger, Director of Government
18 Affairs from Siemens Medical Solutions,
19 representing AdvaMed this afternoon. Thank
20 you for having the opportunity to speak.

21 First, I would like to say that
22 AdvaMed concurs with Bob Britain's points

1 just now, what NEMA said. I think the
2 experience has been pretty consistent in our
3 industry with this program.

4 But I would like to add emphasis to
5 a few of the points that are important to our
6 members. While the program has been received
7 initially by industry with great expectation,
8 of course, to improve the efficiencies with
9 respect to our inspection programs, we're
10 still facing several practical challenges, as
11 Bob noted.

12 First of course is with those
13 manufacturers who have volunteered thus far,
14 they are faced with the difficulty of
15 scheduling the prequalification inspections.
16 And additionally, the entry requirements of
17 the programs themselves are very cumbersome
18 and complex. Both of these issues have
19 frustrated industry, who have -- again, the
20 primary interest of participating in this
21 program to make more efficient their
22 inspectional program. So we hope that FDA

1 will consider those concerns and review those
2 for us.

3 We would like to recognize,
4 however, the effort FDA has taken with
5 respect to implementation of the program. As
6 Bob noted, similar to the third-party review
7 program, every new system implementation
8 takes time and has some bumps on the road,
9 and we hope that we can work together to
10 resolve those issues and move forward with
11 the program.

12 Thank you.

13 MR. BARNETT: Thank you, Diane.
14 Anyone want to respond to that? Anyone in
15 the audience want to respond or have a
16 comment? If not, we'll go to our next
17 speaker, Lindsey Wade, from the National
18 Research Center for Women and Families.

19 MS. WADE: Hi. My name is Lindsey
20 Wade, and I'm a policy associate at the
21 National Research Center for Women and
22 Families. We're a non-profit, non-partisan

1 advocacy center that works to improve the
2 health and well-being of women and children
3 in the United States. I'm here today mostly
4 to remind the FDA that the concerns shared by
5 public health advocates, consumer advocates,
6 and patient advocates about third-party
7 review in 2002 still exist.

8 At the National Research Center for
9 Women and Families, it's our position that
10 third-party inspections weaken safety
11 precautions. To put it more bluntly, the
12 accredited persons program creates an
13 inherent conflict of interest that is
14 unacceptable. The third-party inspectors
15 have little incentive to find problems,
16 because there is no firewall between the
17 inspector and the company that hires them.

18 Manufacturers can attempt to
19 influence the accredited persons with high
20 payments and promises of increased future
21 business. The accredited persons can curry
22 favor by consulting rather than strictly

1 auditing manufacturers and overlooking
2 problems they identify. The client-employer
3 relationship is very different from the
4 inspector-inspectee relationship that should
5 exist in this situation.

6 Accredited persons even promote
7 their ability to improve their client's
8 business, virtually eliminating the
9 possibility that they are unbiased auditors.
10 For example, one AP claims that "Our founders
11 sought out and recruited more of the best
12 auditors in our business because they know
13 that it is auditors that make the difference
14 to you. You will find that our auditors are
15 fair and consistent; they are
16 service-oriented and look for ways to add
17 value to your company."

18 "Our auditors won't tell you how to
19 run your business, they will help you
20 understand the requirements and the various
21 ways you can fulfill them. We will partner
22 with you in order to improve your systems and

1 therefore your bottom line."

2 And from our perspective, the APs
3 aren't supposed to be partners, they are
4 supposed to be inspectors and auditors.

5 Further evidence of the conflict of
6 interest that exists between the
7 manufacturers and the accredited persons is
8 the fact that manufacturers provide
9 accredited persons with testimonials and
10 offer to serve as references to increase
11 their AP's future business. And I just would
12 like to briefly read excerpts from some
13 testimonials.

14 This one is from an American device
15 company to an American accredited persons
16 company. It starts off with: "I feel like we
17 are in a partnership, and I see tangible
18 value to our relationship. We have had
19 assessors at both companies on an annual
20 basis for many years who worked for our
21 former registrar. We had no idea what we
22 were missing."

1 "All your assessors are very
2 thorough and professional and take their
3 responsibility seriously. I felt like they
4 were there not only to assess our companies
5 but to help us become better. They obviously
6 cannot consult, but they can and did offer
7 comments in how others had addressed similar
8 issues. In short, we can't be happier.
9 Please pass along my sincere thanks and
10 congratulations to your entire organization,
11 and feel free to share my comments with
12 others as you feel appropriate."

13 Similarly, another letter commends
14 the AP for an excellent job, and says:
15 "Please do not hesitate to use me as a
16 reference."

17 It's entirely out of character for
18 an inspectee to offer such services to an
19 unbiased inspector. And there is no question
20 that this sort of communication reduces that
21 accredited person's ability to be unbiased.
22 Just to clarify this with an analogy,

1 consider local county public health
2 departments and the inspections of
3 restaurants.

4 Local city and county departments
5 of health are responsible for ensuring that
6 restaurants comply with local ordinances in
7 order to ensure that the restaurants comply
8 with requirements for sanitary food prep
9 areas and other issues. Without these
10 inspectors making inspections on a regular
11 basis to all the restaurants that we go to,
12 we would have no assurance that we're eating
13 food that is safe to eat.

14 If those restaurants were able to
15 hire a private inspector to guide them and
16 partner with them, the public might not ever
17 know about problems that exist in the past or
18 currently with health hazards at that
19 restaurant. With the system with public
20 health employees reviewing restaurants to
21 make sure that there is safe food
22 preparation, there is a public record of that

1 restaurant's behavior, whether it is good or
2 bad.

3 We understand that the Center for
4 Devices and Radiological Health is
5 underfunded and understaffed. However, we
6 would prefer fewer reliable inspections to
7 yearly biased reports from third-party
8 investigators.

9 Thank you for the opportunity to
10 speak today.

11 MR. BARNETT: Thank you, Ms. Wade.
12 Any comments or reactions from the panel?
13 And if that's the case, that's the last of
14 our three.

15 So let me open the floor to
16 comments or reactions to any of the things
17 that you heard during this panel. Anyone
18 want to say anything about this, about
19 third-party inspections? Comments that we
20 haven't heard before? Okay, if that's the
21 case, we're ready then for the next session.

22 Steve, thank you.

1 MR. NIEDELMAN: Thank you.

2 MR. BARNETT: We'll call up Ginette
3 Michaud from the Office of Device Evaluation
4 at CDRH, and we're going to be talking now
5 about reprocessing of single-use devices.
6 And our first speaker is Naomi Halpern from
7 the Association of Medical Device
8 Reprocessors. Naomi?

9 MS. HALPERN: I'm sorry. Hi, I'm
10 sorry to keep you waiting. I'm Naomi
11 Halpern. I'm an attorney specializing in
12 providing advice to companies and individuals
13 with respect to the regulation of medical
14 devices and pharmaceuticals by the United
15 States Food and Drug Administration. My
16 firm, Olsson Frank and Weeda, is regulatory
17 counsel to the Association of Medical Device
18 Reprocessors, or AMDR.

19 AMDR is the trade association
20 representing the legal, legislative and
21 regulatory interests of third-party
22 reprocessors of medical devices labeled for

1 single use. AMDR's members represent
2 approximately 95 percent of the commercial
3 reprocessing industry.

4 It's worth reiterating what we've
5 said in the past, which is that prior to the
6 enactment of MDUFMA; reprocessors were
7 already subject to the same regulatory
8 requirements as original equipment
9 manufacturers. The safety record of
10 reprocessing has always been and continues to
11 be excellent. Today, more than 30 million
12 devices have been reprocessed and used in
13 this country without any evidence of
14 increased risk to patients.

15 The fact that certain devices
16 labeled by their original manufacturers as
17 being for single use that can safely be
18 reprocessed is widely recognized by the
19 clinical community, which has repeatedly
20 expressed overwhelming support for and
21 confidence in the safety of the reprocessed
22 devices.

1 Reprocessors use state-of-the-art
2 validated procedures to clean, sterilize, and
3 restore their devices, and every device is
4 tested or inspected before being returned to
5 service.

6 America's finest medical facilities
7 use reprocessed devices, including 13 of the
8 14 hospitals ranked by U.S. News and World
9 Report in 2004 as America's top hospitals.
10 These institutions include Massachusetts
11 General, Brigham and Women's Hospital, The
12 Mayo Clinic, The Cleveland Clinic, and Johns
13 Hopkins University. It defies belief to
14 argue, as some have and continue to do, that
15 these fine institutions would put their
16 patients at risk in order to save money.

17 To the contrary, these facilities
18 use reprocessed devices because they have
19 studied the issue thoroughly and they have
20 determined that reprocessing is safe.

21 In light of the strict regulation
22 that was in place at the time that MDUFMA was

1 enacted, and in light of the safety record of
2 reprocessing, it is difficult to find any
3 public health rationale for MDUFMA's
4 reprocessing provisions.

5 Rather, it seems entirely clear
6 that economics were the driving force behind
7 these provisions, which were the product of
8 OEM's continuing frustration with the
9 economic threat posed by reprocessing.
10 Nevertheless, MDUFMA does contain some
11 important messages about reprocessing.

12 First, Congress clearly stated that
13 there are cost savings associated with using
14 reprocessed devices. Therefore, Congress
15 said, we want to ensure continued access to
16 safe and effective reprocessed devices.

17 Second, Congress intended that
18 MDUFMA be implemented in the least burdensome
19 manner consistent with FDAMA. AMDR has seen
20 its role over the past year as being in part
21 to keep reminding regulators of these
22 objectives as the Agency goes about

1 implementing the statute.

2 So where are we now? FDA continues
3 to implement MDUFMA, and reproprocessors are
4 complying with the requirements.

5 First, I would like to talk about
6 the MDUFMA-imposed requirement that
7 reproprocessors make supplemental validation
8 submissions for some of their previously
9 cleared devices. Despite feeling that the
10 requirement may not have been implemented in
11 the least burdensome manner, as required by
12 FDAMA, our members have complied with this
13 new requirement, and FDA has completed its
14 review of most of these submissions.

15 Much more than the typical 510(k)
16 submission, the process of submitting
17 validation data has been an exercise in
18 working with the Agency to determine what a
19 submission was going to have to contain and
20 what it was going to have to look like. The
21 process of clarifying and responding to
22 questions about submissions occurred in the

1 context of a very tight deadline for
2 concluding the process. An enormous amount
3 of work was required to gather the
4 FDA-required information.

5 At the end of the day, many of the
6 submissions were cleared by the Agency. For
7 the submissions that were not cleared, AMDR's
8 members ceased shipping the devices that were
9 covered by those submissions. But AMDR's
10 members estimate that more than 95 percent of
11 their products lines were made legally
12 marketable.

13 We are aware that OEMs have
14 continued to assert that the issuance of "Not
15 Substantially Equivalent," NSE letters, to
16 the reprocessors just confirms their
17 oft-stated allegation that it is not possible
18 to establish that the reprocessing of some of
19 these devices is safe and results in
20 effective devices.

21 I want to remind you that all of
22 these devices were previously cleared by the

1 Agency. Safety was not the issue. And in
2 fact, the Agency has publicly clarified that
3 the fact that a particular submission was not
4 cleared before the deadline does not mean
5 that the devices were unsafe in FDA's
6 opinion.

7 The issuance of an NSE letter means
8 only that to date, the data and information
9 submitted were not sufficient to support a
10 finding of substantial equivalence, and
11 therefore, to be cleared by FDA. Indeed in
12 some cases, the NSE letters reflected nothing
13 more than the lack of sufficient time to
14 develop and submit the information due to the
15 Agency's imposition of a non-statutory
16 deadline.

17 In other cases, NSE letters were
18 issued because the reprocessor did not make a
19 submission or withdrew an initial submission
20 after making a business decision that the
21 economics of the market did not justify the
22 expenditure of the substantial resources that

1 would be required by the SVS process.

2 In short, as a factual matter, an
3 NSE letter does not establish that the device
4 covered by the letter is not safe or
5 effective, and there is clearly no
6 justification for the assertion that an NSE
7 letter is evidence that the submitter is not
8 capable of producing a safe or effective
9 device.

10 Over the last year, AMDR's members
11 have continued to work cooperatively with the
12 Agency, and many of the submissions that were
13 initially designated NSE have now been
14 cleared. In the past year, of course,
15 certain OEMs have continued their efforts to
16 persuade Congress to revisit the marking
17 provision of Section 301 of MDUFMA, and
18 specifically to apply that provision only to
19 reprocessors.

20 It's worth remembering that when
21 Congress was in the process of drafting
22 MDUFMA, FDA took the position that marking of

1 devices would have value, and in fact, it
2 would be helpful from a regulatory point of
3 view if all devices were marked. At the
4 time, OEM industry representatives were
5 willing to commit to doing that.

6 MR. BARNETT: Two more minutes.

7 MS. HALPERN: Congress, when
8 enacting the provision, specifically
9 emphasized that the section applies to all
10 devices, not just single-use devices. OEMs
11 afterwards recognized that complying with the
12 provisions would be burdensome, and for that
13 reason, OEMs returned to Congress to ask them
14 to amend Section 301 to apply only to
15 reprocessors. Congress yielded to this
16 pressure, and the Act was so amended.

17 AMDR's members will comply with and
18 flourish under the additional regulatory
19 burdens. In the last year, we have seen
20 further efforts from the OEMs to use the
21 regulatory process to further their economic
22 agenda. Specifically, there have been

1 several petitions from trade associations
2 asking FDA to add more devices to the lists
3 of reprocessed devices that require the
4 submission of validation data.

5 In general, we believe that these
6 requests have failed to include any credible
7 public health rationale. In the last few
8 months, FDA has, in response to these
9 petitions, added heart positioning devices
10 and endoscopic and microscopic devices to the
11 list of devices that require 510(k)s with
12 validation data. AMDR's members do not
13 oppose the requirement for 510(k)s for heart
14 positioning devices.

15 But AMDR believes that in fact, all
16 heart positioning devices should be subject
17 to 510(k) requirements. The exemption for
18 heart positioners appears to be based on the
19 fact that they are covered by the same
20 classification regulation as forceps,
21 retractors and other relatively simple
22 devices.

1 However, the heart positioners and
2 stabilizers of today are much more
3 complicated devices that allow a surgeon
4 actually to lift and turn the heart. The
5 failure of such a device during surgery,
6 whether it is reprocessed or not, could
7 easily cause serious injury to a patient, and
8 the AMDR urges FDA to consider up-classifying
9 all of these devices and requiring 510(k)s
10 for all of them.

11 Apart from heart positioners, AMDR
12 strongly urges FDA to preserve the 510(k)
13 exemption for all currently exempt
14 reprocessed single-use devices, and to
15 decline to require SVSes for additional
16 devices. Finally, this year, we have seen an
17 upswing in activity on the state level to
18 enact legislation to burden reprocessing.

19 Typically, the OEMs involved in
20 pushing these efforts suggest to legislators
21 that despite the stellar safety history of
22 reprocessing, these bills are necessary

1 because safety of reprocessing cannot be
2 established. Although they have not to our
3 knowledge provided legislators with actual
4 examples of patient harm, they have
5 distributed photographs that purport to
6 establish that reprocessed devices may not in
7 fact be clean. In fact, they may show you
8 these photographs today.

9 However, to date, these OEMs have
10 to our knowledge been unable or unwilling to
11 authenticate these photographs, and the
12 bottom line is that there is no credible
13 evidence that devices reprocessed in
14 compliance with FDA requirements present any
15 risk to patients beyond the risk that is
16 associated with reprocessed devices. Let me
17 skip through most of this and just finish up.

18 I do want to say that one aspect of
19 the state level activity is informed consent
20 provisions. The purpose of informed consent
21 is to advice patients when a procedure
22 involves increased risk. However,

1 reprocessed devices are as safe and effective
2 as the original equipment, and are in fact
3 arguably more stringently regulated.

4 Therefore, there is no legal, medical, or
5 ethical basis for imposing informed consent.

6 That said, AMDR does not oppose
7 state-level informed consent legislation that
8 honestly seeks to increase patient awareness
9 of medical device safety. Such a bill would
10 apply equally to OEMs, many of whom have
11 recently experienced serious safety problems
12 associated with their own devices.

13 Just a few weeks ago, FDA announced
14 that it had seized devices manufactured by
15 one major OEM because FDA inspections had
16 revealed that the firm is continually out of
17 compliance with GMPs. A few months ago,
18 another OEM acknowledged that it knew, that
19 it had not told doctors or patients for three
20 years about a flaw in its device.

21 Let me just say that reprocessing
22 saves hospitals substantial amounts of money.

1 It's good for patients, it's good for
2 hospitals, it's good for the environment.
3 The good news for hospitals is that despite
4 the additional regulatory burdens that have
5 been increasingly placed on the industry,
6 reprocessing is continuing to flourish and
7 also to drive prices down of original
8 equipment itself.

9 In short, reprocessing plays a
10 vital role in our health care system because
11 it is one of the few ways that hospitals can
12 achieve substantial cost savings while
13 maintaining the absolute highest standard of
14 patient care. The implementation of MDUFMA
15 has presented some new hurdles this year,
16 hurdles that the industry does not believe
17 are warranted, but they are hurdles that the
18 industry is meeting and will continue meeting
19 in the coming year. Thank you.

20 MR. BARNETT: Thank you, Naomi.
21 Anyone on the panel want to respond or ask a
22 question? Anyone in the audience? Okay, if

1 that's the case, let's go into our next
2 speaker from AdvaMed, Tony Blank.

3 MR. BLANK: Good afternoon. I have
4 two promises: One, I'll make sure I finish
5 on time; second, I have no gross pictures.
6 Just one response to the comments before with
7 regards to the provision of validation data,
8 is where data that under the quality system
9 regulation one would expect any medical
10 device manufacturer to have in their files
11 and at their fingertips and ready to be
12 bundled into submission.

13 So when I put together the outline
14 for this, I thought a little bit about the
15 attempts my little brother has given to me to
16 teach me the game of golf. He has told me
17 that I have made significant progress,
18 although I still have some lingering
19 challenges, and one of the things I need to
20 work on is my follow-through.

21 So progress that has been made.
22 There was a Congressional mandate in MDUFMA,

1 lots of changes came as a result of that; for
2 example, there were revisions to the MedWatch
3 form to capture the reprocess status of a
4 device if there was an event associated with
5 it. FDA has issued numerous guidance
6 documents to provide direction to industry on
7 reprocessing.

8 They have done a marvelous job, I
9 would say, and should be congratulated for
10 the vast rapid review of the supplemental
11 validation data submissions. There have been
12 some exemption terminations which we as
13 AdvaMed believe are warranted and valid for
14 very valid reasons.

15 And with the recent MDUFSA
16 legislation, there was a narrowing of the
17 Section 301 provisions to reprocess
18 single-use devices.

19 So sort of significant progress has
20 continued in terms of the continued review
21 and termination of exemptions when warranted;
22 for example, stone dislodgers, orthodontic

1 brackets. There have been continued reviews
2 and calls for supplemental validation data,
3 again, I believe when warranted, specifically
4 endoscopic accessories and heart stabilizers.

5 There are some lingering
6 challenges, however. There is, as you can
7 imagine, continued pressure on FDA from a
8 variety of stakeholders: The OEMs, the
9 hospitals, the reproprocessors. There is a
10 tremendous amount of education that must
11 continue, I think, that needs to be balanced
12 and fair. For example, if a single-use
13 device fails after it has been reprocessed,
14 there can be no underlying problem with the
15 original device.

16 So if the product was designed,
17 manufactured, labeled as a single-use device,
18 and it made it through the single-use and it
19 was subsequently reprocessed and that device
20 failed, there was nothing wrong with the
21 single-use device. Any failure, by
22 definition, is associated with the

1 reprocessing. Period.

2 If a reprocessed single-use device
3 fails or there is an event, the report must
4 always go to the reprocessor. Another
5 significant challenge that lingers is proper
6 AMDR reporting. As I said, there has been a
7 change to the MedWatch form. However, we
8 have to admit and recognize, I believe, that
9 there is an inherent disincentive for the
10 user facilities to acknowledge, when
11 reporting events, that the event was
12 associated with the device that had in fact
13 been reprocessed.

14 And frankly -- which gave birth to
15 the Section 301 provisions at the
16 beginning -- there is an inherent lack of
17 awareness by physicians and by health care
18 practitioners generally and by patients as to
19 whether or not the device that is used on
20 them has in fact been reprocessed.

21 So working on the follow-through,
22 we think it's important, and in fact it is

1 critical, that we continue to follow-through
2 as Congress has intended. There is a quote
3 from the House report; here is a quote from
4 the Senate report, from the recent
5 legislation, and I won't read it to you.

6 However, at the very beginning, the
7 Senate is very explicit: "Reprocessed
8 single-use devices are not generally marked
9 to identify the reprocessors. Adverse events
10 associated with the reprocessed device may
11 therefore be misattributed to the original
12 manufacturer, not to the reprocessor." The
13 reason these provisions to Section 301 have
14 been introduced is to lead to the marking of
15 reprocessed single-use devices.

16 The Senate has stated that the
17 reason for this provision is to ensure that
18 the practitioners and the hospital
19 administrators know that the device that they
20 are using has in fact been reprocessed, and
21 it cannot work as intended unless health care
22 providers, original manufacturers, device

1 reprocessors and FDA can readily and
2 accurately identify when an SUD has been
3 reprocessed. This is also taken straight out
4 of the Senate report language.

5 The Senate recognized that there
6 has been, associated with the failure to
7 accurately identify reprocessed devices,
8 inadequate reporting, which fundamentally
9 challenges the underlying cornerstone of
10 FDA's post-market surveillance system.

11 Congress believes, believed, and
12 continues to believe there is no reason for
13 FDA to delay implementation of this
14 provision, and the committee expects
15 reprocessors to implement its requirements as
16 soon as possible.

17 So in sum, great progress, not sure
18 my brother would say that about my golf game.
19 However, challenges do remain, but patient
20 safety, regardless of any pressure from
21 anybody else, must always be tantamount and
22 first. And that's it. Thanks.

1 MR. BARNETT: Thank you, Tony.
2 Does the panel have any response or questions
3 for Tony? Anyone in the room want to say
4 anything? If that's the case, let's go to
5 our final speaker, Mark Leahey, from MDMA.

6 MR. LEAHEY: Thanks Mark, and I
7 promise this is the last time I will be
8 getting up today. I want to, I think, go a
9 little beyond what Tony mentioned. I think
10 he highlighted a lot of the important steps
11 that had been taken to ensure patient safety
12 in this area. But I want to specifically
13 focus on FDA's recently published draft
14 guidance for industry and staff, entitled
15 "Compliance with Section 301 of the Medical
16 Device User Fee and Modernization Act of
17 2002," as amended prominent and conspicuous
18 marks manufacturers' single use devices.

19 Now, before I go further, I think
20 that this is a critical moment here, probably
21 the first in the three years that I have been
22 participating in these stakeholder meetings,

1 that I 100 percent agree and am aligned with
2 FDA's position on this.

3 MDMA agrees with FDA's
4 interpretation of Section 502(u) of the Food
5 and Drug Cosmetic Act as amended by MDUFMA,
6 which requires manufacturers of reprocessed
7 SUDs to mark the reprocessed device
8 prominently and conspicuously, with the name
9 of the reprocessor, a generally recognized
10 abbreviation of such name, or unique and
11 generally recognized symbol identifying the
12 reprocessor.

13 Section (v) (2) of the FDA guidance
14 document outlines the effective date for
15 implementing the reprocessor labeling
16 requirements of Section 502(u). According to
17 the guidance document, if the original
18 equipment manufacturer first marks the device
19 with its name or symbol before
20 August 1, 2006, the reprocessor must mark the
21 reprocessed device by August 1, 2006.

22 If the OEM first marks the device

1 after August 1, 2006, the reprocessor must
2 immediately mark the device. MDMA agrees
3 that the approach described in the FDA
4 guidance document clearly reflects the
5 language of the statute, and ensures the
6 legislation's goal of protecting patient
7 health is fulfilled as expeditiously as
8 possible.

9 Congress has repeatedly recognized
10 that unmarked reprocessed SUDs may pose
11 significant patient safety risk. When the
12 reprocessor of an SUD is not identified, the
13 FDA is prevented from adequately identifying
14 and controlling the risk posed by
15 reprocessing. FDA's NDR regulations are the
16 cornerstone of FDA's post-marketing
17 surveillance system for medical devices, as
18 Tony mentioned. These regulations require
19 manufacturers to report patient injuries and
20 product malfunctions to FDA.

21 This information enables both the
22 manufacturer and FDA to identify the safety

1 and/or effectiveness problems, and to take
2 any needed corrective action. Sometimes
3 these protective actions include recalls or
4 other notifications to the field to prevent
5 unnecessary patient injuries. This system
6 cannot work unless the health care providers,
7 the OEM and the FDA can readily identify when
8 and whom a SUD has been reprocessed.

9 Unless reprocessor devices are
10 clearly marked as such and the reproprocessors
11 clearly identified, the OEM will likely be
12 erroneously identified as a source of a
13 reprocessed device. This may significantly
14 hinder or preclude FDA's ability to identify
15 and address safety and efficacy failures
16 associated with reprocessed SUDs. In light
17 of these serious public health concerns,
18 Congress required reproprocessors to mark their
19 reprocessed SUDs by August 1, 2006, within
20 one year after the implementation of the Act.

21 Further, Congress indicated that
22 the reproprocessors should mark their devices as

1 soon as possible. Congress suggested that it
2 should not take reprocessors a year to mark
3 their reprocessed devices, and discouraged
4 reprocessors from taking the entire year to
5 comply.

6 Specifically, in the MDUFSA report,
7 the committee stated, "Although Section
8 502(u) will first become effective twelve
9 months after the legislation is enacted, the
10 committee believes that it is clear how this
11 section applies to the vast majority of
12 reprocessed devices. And the committee
13 expects reprocessors to implement these
14 requirements as soon as possible for the
15 devices they reprocess, in the best interests
16 of post-market surveillance and the public
17 health."

18 In other words, reprocessors were
19 on notice as of August 1, 2005, that devices
20 currently on the market and for products
21 under development that the marking of devices
22 is a component of their required product

1 manufacturing, labeling development and
2 intake procedures to identify when a
3 previously used device is marked.
4 Reprocessors were given a full 12 months to
5 do so. The vast majority of devices that are
6 reprocessed require 510(k) pre-market
7 notification clearance prior to marketing.

8 This requires reprocessors to
9 develop and implement reprocessing
10 procedures; develop and print product labels,
11 labeling and packaging, and to ensure that
12 their manufacturing practices are in full
13 compliance with FDA's QSR before the
14 reprocessed device is ever marketed.

15 Marking the device with a
16 reprocessor's name or symbol, in addition to
17 other product labels and labeling that must
18 be developed, is a relatively minor aspect of
19 this process, and certainly does not require
20 an additional year to implement after
21 receiving clearance for marketing.

22 There is no justifiable reason for

1 permitting a reprocessor a year of anonymity
2 to hide from regulatory requirements
3 specifically designed to protect patient
4 safety. Under these circumstances, if the
5 concept of allowing reprocessors an
6 additional year to mark their reprocessed
7 devices has been a part of the discussions
8 between industry, patient advocacy
9 organizations, FDA and Congress in the
10 developing of MDUFMA amendments, industry and
11 the patient advocacy organizations would have
12 strongly objected and urged Congress not to
13 adopt this approach.

14 Therefore, I want to again
15 encourage and commend the FDA for the initial
16 draft guidance. And in closing, I want to
17 say again it's an area where MDMA certainly
18 supports FDA's position on this, and I think
19 it's certainly in the best interests of
20 patient safety.

21 Thank you.

22 MR. BARNETT: Thank you, Mark.

1 Anyone on the panel want to respond or ask
2 questions? If that's the case, before we
3 close this panel, is there anyone in the
4 audience that wants to say anything, or react
5 about this particular issue of reprocessing
6 single-use devices?

7 Okay, that being the case, we're
8 ready for a break. It's listed on the
9 schedule as 15 minutes. I have 1:25, so why
10 don't we say about 20 minutes to 2:00.

11 (Recess)

12 MR. BARNETT: We're ready to go
13 into our sixth session, on other provisions,
14 and we have our standing FDA panel here:
15 Linda, Joanne, Diane and Bob. And we have
16 added to that Pat Love, who's here with the
17 Office of Combination Products in FDA, and
18 she's here in place of Mark Kramer, who
19 couldn't come, and Steve Sykes, who's with
20 the Office of Surveillance and Biometrics in
21 CDRH.

22 And our first speaker, a constant

1 lead-off speaker, Bob Britain from NEMA.

2 MR. BRITAIN: Pat, I'm not going to
3 say anything bad.

4 MS. LOVE: You're allowed.

5 MR. BRITAIN: Just a very brief few
6 words about combination products. I think
7 you all know what combination products are.
8 This isn't a new issue; it's been at FDA for
9 many, many years: Drugs and devices.
10 Medical imaging devices and contrast agents
11 are used together. Contrast agents improve
12 or enhance the image of x-ray, of magnetic
13 resonance, of ultrasound. And it's been a
14 problem in the past, because obviously,
15 combination products means two different
16 agencies that you're working with.

17 And the problem is the focus. You
18 need a focus at FDA, so when we had the
19 opportunity to work with FDA and the Capitol
20 Hill staff, everyone was pretty excited about
21 the possibility of putting an Office of
22 Combination Products together. And we worked

1 very hard to push this through because it's
2 pretty hard to get legislation that sets up
3 offices. It's not easy.

4 So we had very high expectations
5 when MDUFMA was passed and signed into law.
6 It gave the Secretary the authority to set up
7 this Office of Combination Products. And we
8 obviously had high hopes that it would
9 improve the approval process of contrast
10 agents with their use with MRI, et cetera,
11 ultrasound. And after many meetings with the
12 Office of Combination Products -- and I must
13 say the Office of Combination Products has
14 met with us on many occasions -- it's working
15 with us to try and see this through.

16 But we were finally advised that we
17 were a concomitant product instead of a
18 combination product, which kind of took the
19 wind out of our sails, because we probably
20 wouldn't accrue the same benefits and
21 efficiencies that we would have been if we
22 were a combination product.

1 The interesting thing is, when we
2 were working on the legislation, everybody
3 thought this was a combination product, the
4 medical imaging and contrast agent.
5 Everybody. The Hill staff, industry.

6 So my only reason for being here
7 and spending a couple of minutes with you is
8 not to offer any solutions, because we intend
9 to keep working with the Office of
10 Combination Products. They seem to be happy
11 to continue to work with us even though we're
12 not a combination product. And so my only
13 reason to be here and tell you about this is
14 that it's a solution that MDUFMA did not
15 bring to us that we worked very hard to get.
16 And Pat, we will continue to work through
17 this. We don't know what the final solution
18 will be, but I think we'll get there.

19 MR. BARNETT: Thank you, Bob.
20 Anyone want to respond to that?

21 MS. LOVE: I just like to ask a
22 question, please, Bob. Certainly the

1 definition of combination products, those
2 that are separately provided under 3.2(e)(3),
3 talks a bit about mutually conforming
4 labeling and how things are specifically
5 identified. And as you alluded to, imaging
6 agents are not necessarily labeled in that
7 way. It's possible, but most of them aren't
8 at this point.

9 Do you have some general thoughts
10 or recommendations? I know you said you
11 didn't have a definite recommendation under
12 MDUFMA, but do you think that issues such as
13 this that might relate to classes of products
14 that are often used together, either
15 off-label or maybe there are co-development
16 questions -- do you feel that this is
17 something that should in some way be
18 addressed in MDUFMA, or are these things that
19 should be addressed as in the course of
20 providing the guidance, some of the issues
21, about the quality aspect of things that were
22 mentioned earlier?

1 Is this a guidance approach issue?
2 Is this something that you see in
3 clarification of mutually conforming labeling
4 issues? Where might this fall as a class
5 concept? Sorry to put you on the spot.

6 MR. BRITAIN: I don't know. I
7 should have said the reason this is so
8 important -- to find a solution. I don't
9 know where it is in guidance or pushing
10 contrast agent manufacturers harder and
11 faster to get these things approved -- but
12 the problem is the using community, the
13 radiologists, et cetera, that use MRI and CT
14 and ultrasound use contrast agents that are
15 not labeled to be used with MRI or CT, and so
16 the manufacturers of the equipment cannot
17 label or train the users because this is
18 off-label use.

19 And so this is why it's so
20 important to find a resolution, because the
21 real world is -- they are being used together
22 unapproved.

1 Pat, I'm sorry, I just don't have a
2 solution for you.

3 MR. BARNETT: Anyone else on the
4 panel want to respond or comment? Someone in
5 the audience? If that's the case, let's call
6 our next speaker, who's Jack Lasersohn from
7 the National Venture Capital Association.

8 MR. LASERSOHN: Thank you very much
9 for inviting us to attend. I'm Jack
10 Lasersohn, and I'm a general partner at the
11 Vertical Group, which is a major medical
12 device venture capital firm. I'm past
13 chairman of the medical industry group at the
14 National Venture Capital Association, which
15 is the national trade association of the
16 venture capital community. Now, in this
17 talk, since this is the first time that we
18 have really presented in front of the FDA
19 stakeholder meeting, we really wanted to just
20 introduce who we are to a large extent to the
21 FDA, and put some context around why we have
22 a somewhat different view of some of these

1 issues than perhaps the rest of the industry.
2 That's what this talk will focus on.

3 By way of background, the National
4 Venture Capital Association is 500-member
5 venture capital firms. We have approximately
6 \$100 billion under management at any given
7 time.

8 We're investing about \$20 billion a
9 year in high technology start-ups, primarily
10 in the United States. Most of you probably
11 think of us as people who do the internet and
12 semi-conductors and computers. And that is
13 true, that is still about 60 to 70 percent of
14 the venture capital money flows. But in
15 addition, we have financed, for example, the
16 entire biotechnology industry, and
17 historically probably about 50 percent of all
18 medical device firms today. We're founded
19 with venture capital money.

20 About 100 million Americans have
21 benefited from the investment the venture
22 community has made in medicine over the last

1 25 years. Twenty-five million, we believe,
2 conservatively, have had their lives extended
3 or quality of life improved every year
4 through the use at this moment of technology
5 originally developed by companies funded with
6 venture capital. These are some of the areas
7 that we have made very significant
8 investments in. Heart disease has been a
9 leading area.

10 We did create, we founded the first
11 angioplasty companies in the 1980s, founded
12 the minimally invasive heart bypass, all of
13 the electroablation companies, first
14 implantable cardiac defibrillators, automatic
15 external defibrillators, and then
16 biotechnology, many, many drugs, including
17 ReoPro, Integrilin, tPA. In imaging, we
18 founded the first superconducting MRI
19 systems, the first ultrasound systems, the
20 first Doppler ultrasound systems, as well as
21 many other drugs for cancer.

22 So our activities are very broad

1 within the health care space. As I said,
2 medical devices in biotechnology make up
3 about 25 to 30 percent of all venture capital
4 activities right now, medical devices about
5 10 percent. And that's out of an annual
6 money flow of about \$20 billion a year. So
7 about \$2 billion to \$3 billion a year right
8 now from the venture industries going into
9 medical device technology.

10 These are the first financing, so
11 these are classic start-up financings in the
12 life sciences area, including biotechnology.
13 They are pretty steady, at about 200 per
14 year. These are first financing, so start-up
15 companies in that segment. These are the
16 number of first financings in medical
17 devices -- '05 second quarter is an
18 aberration. It's historically been about 100
19 companies a year, so very, very active.
20 These are again start-up companies, first
21 financings for start-up companies in medical
22 devices.

1 The investment that we're making
2 has continued to grow, it did peak in 2000
3 and 2001. But even in 2002 and today, it's
4 much, much higher than it was historically,
5 and we project that it will continue to
6 increase. The number of companies is very
7 steady. Again, this is total financing for
8 companies, not just start-up companies.
9 Second round financings, financings as they
10 get more mature, but 4- to 700 per year is
11 very typical of the number of companies in
12 the medical and life sciences area that's
13 been financed exclusively essentially by the
14 venture capital community.

15 And within that, the medical device
16 sector continues to be very strong, about \$2
17 billion a year in all medical device
18 companies for venture capital, anywhere from
19 \$400 to \$500 million per quarter. One of the
20 points I would like to make that's very
21 important is that the funding requirements
22 for medical devices has just increased

1 dramatically, partly because of the
2 complexity of the technology, but also
3 because of the regulatory hurdles.

4 We started the first angioplasty
5 company in 1980. It cost \$3 million to get
6 it to profitability, and then it was sold to
7 Eli Lilly. A very, very similar technology,
8 in fact simpler technology balloon,
9 kyphoplasty, we started in 1994, took
10 \$75 million to get to the same point. That
11 number continues to grow dramatically.

12 One of the key points I think we
13 need to make is that we're investing in
14 revolutionary medical technology by
15 definition.

16 We will not fund VC technology as
17 much as it might be very important to evolve
18 technology along the line. Big companies do
19 that incredibly well, much better than we
20 can. So we're investing almost exclusively
21 in revolutionary technology, so the first
22 angioplasty company, the first MRI, the first

1 pulse oximetry, first ablation, ICDs,
2 neurostimulation, triple As. These were all
3 started by the venture capital community.

4 As a result of the novelty, we face
5 peculiar problems, different problems.
6 Often, the staff of the FDA has never seen
7 the type of device that we're talking about.
8 So we have an enormous learning curve hurdle
9 to get over with the FDA. There's always a
10 lack of precedence and pathways, and in some
11 cases, there are precedents that actually
12 hurt us.

13 I mentioned before that sometimes
14 having guidances can be difficult because we
15 have to get ourselves out of a particular
16 guidance pathway because what we're doing
17 really doesn't fit.

18 And we always face a tremendous
19 problem in clinical trial design and
20 interpretation because of the novelty factor.
21 So this brings a -- we really do have a
22 different emphasis -- not better, just

1 different -- than the rest of the industry.
2 And our focus is going to be on solving these
3 problems. To give you some idea of just the
4 kinds of things that we're doing right now, I
5 took a survey of the venture community.

6 And this is a snapshot in time
7 today of sort of what the venture community
8 is working on, you will see that many of
9 these things -- not all of them, but many are
10 things the FDA has never seen before.

11 So the very first spinal nucleus
12 replacements are going to be produced by the
13 venture community. They are going to be
14 showing up at the FDA. They are showing up
15 at the FDA right now and will be very
16 challenging. All of these are different in
17 kind than the types of products that you are
18 used to seeing. We agree with everything
19 that has been said before about the need for
20 transparency and consistency and
21 predictability.

22 We are very much in favor of fees.

1 We have no problem paying fees if they are
2 based on performance. Our companies do have
3 money. Even though they are start-ups, they
4 are well-funded. They will pay for fees if
5 that will shorten the regulatory or improve
6 the regulatory outcomes. We do believe that
7 the whole concept of least burdensome is very
8 important, and our intention is in fact to,
9 as part of the MDUFMA process, to revisit
10 this.

11 MR. BARNETT: Two more minutes,
12 please.

13 MR. LASERSOHN: Thank you. At the
14 statutory level. We've tested this concept,
15 we think it really can work, and we're going
16 to be asking to think more about how to bring
17 the least burdensome process forward.
18 Obviously, we agree with meeting management.
19 All of the things that have been said before
20 about quantitative results are certainly
21 supported by us. I have also said that we
22 are in favor of new processes, particularly

1 for novel products.

2 I don't mean expedited processes, I
3 just mean processes that are able to draw in
4 different resources that have a different
5 pathway, not in terms of safety and
6 effectiveness, but in terms of the types of
7 pathways through the FDA.

8 We do think that HDEs are an area
9 that we should return to focus on. A draft
10 guidance has essentially shut down the HDE
11 process at the moment, requiring that sub
12 populate -- that you can essentially not have
13 off-label use is a matter of physical
14 reality.

15 We think that that is not a good
16 decision by the FDA. We would like to
17 revisit that. We think that creates an
18 opportunity for another pathway for truly
19 novel devices that really may not be able to
20 be approved through existing regulatory
21 pathways.

22 We support the critical path

1 initiatives. We want to collaborate with the
2 FDA in trying to define that. And our
3 intention going forward is to be as actively
4 engaged with FDA as possible and defining
5 some of these new ideas. Thank you.

6 MR. BARNETT: Thank you. Anyone on
7 the panel want clarification, have a
8 question? Yes.

9 MS. LESS: I just want to ask you,
10 what did you mean by continuous medical
11 application? Is that what you were talking
12 about earlier, risk-based approach?

13 MR. LASERSOHN: I don't know if I
14 used the word "continuous." If I did --

15 MS. LESS: It was on the slide.

16 MR. LASERSOHN: Continuous was
17 probably a typo. The risk-based approach, if
18 that's what you're asking about, is again to
19 try to have a process that
20 defines -- particularly for the staff, not so
21 much for the higher level -- at CDRH, which I
22 think understands this concept well. That

1 defines for the staff ab initio at the
2 beginning of the process; that is, in pre-IDE
3 discussions, that decisions about the pathway
4 should be made consciously with a particular
5 level of risk in mind.

6 That is, if a device comes in that
7 really has proven to be, through feasibility
8 studies, for example, very likely to be very
9 low-risk, the level of evidence of
10 effectiveness should be adjusted accordingly.
11 And we have found -- and this is just one
12 narrow point, but we have found that this is
13 a -- that process, that discussion has taken
14 very often months or years to cycle with
15 acceptable results at the end, but has taken
16 a long time to get to the proper result.

17 MR. BARNETT: Any other questions
18 from panel? If not, thank you. And let's go
19 to our next speaker, Diana Zuckerman, of the
20 National Research Center for Women and
21 Families.

22 MS. ZUCKERMANN: While we're

1 waiting for the slides, I can say thank you
2 very much for the opportunity to be here.
3 I'm Dr. Diana Zuckermann. I'm president of
4 the National Research Center for Women and
5 Families. And here is my slide. Our center
6 is a non-profit research center, and we use
7 research information to work for programs and
8 policies that improve the health and safety
9 of women, children and families.

10 Just for a little background, my
11 background is as an epidemiologist, and I've
12 worked on Capitol Hill doing oversight on FDA
13 issues, so these are issues of particular
14 interest to me. And although there are not
15 too many consumer-oriented non-profits here
16 today, there are a lot of consumer-oriented
17 non-profit organizations that we work with on
18 these issues. And although they were not
19 able to be here today, we have been working
20 in coalition with them, and they do care a
21 lot about this particular legislation, even
22 though they weren't able to be here today.

1 These are the healthy people that
2 we do research on. These are the people in
3 clinical trials in the PMAs. And so these
4 are the people that are very often studied
5 for hip replacements, or sometimes heart
6 valves and so on.

7 These are what I like to think of
8 as my baby boomer friends. And those of us
9 who are baby boomers know that there are lot
10 of spare parts that a lot of us are using.
11 And we're pretty healthy. And we use them
12 and we're very happy to have these medical
13 devices.

14 However, these medical devices
15 don't always last that long, and so one of
16 the concerns that we have about MDUFMA is to
17 make sure that resources are allocated in a
18 way that helps make sure that products are
19 safe for long-term use and that we know what
20 the long-term risks are. Because one of
21 these days, those of us who look like this
22 now, 10 or 20 years later or a little bit

1 more, are going to be the frail elderly. And
2 if those devices, if those hip replacements
3 or breast implants or whatever they are start
4 to fail, those people might be in a situation
5 where they're not healthy enough to have them
6 surgically removed and replaced at that time.

7 So that's one of the reasons why we
8 think that the long-term safety of many
9 medical devices are really very crucial.
10 Even if they last a long time and are very
11 good in the short run, we need to be aware of
12 what's going to happen in the long run, and
13 people need to know so that they can plan
14 accordingly.

15 So for example, if somebody knows
16 that a hip replacement is likely to fail
17 after some number of years, they might want
18 to have that hip replaced while they're still
19 healthy enough to have the surgery instead of
20 waiting to a point where they're too frail
21 and not able to do that.

22 In the guidance for industry, the

1 FDA had issued this guidance, as you know, in
2 September, regarding race and ethnicity data,
3 and the focus I'd like to talk about today is
4 the differences between who uses devices and
5 who it's studied on. The guidance for
6 industry specified that race should be
7 categorized the same way that it is for other
8 HHS agencies.

9 The FDA does not have regulations
10 or guidance that require adequate
11 participation levels, however, of either
12 racial and ethnic groups or age groups, or
13 sometimes even women and men.

14 So we have a situation where
15 people -- according to the guidance, there is
16 some suggestion of how people be categorized.
17 But there can be zero people in some of those
18 categories. And I have seen that -- in
19 looking at data for PMAs, I have seen
20 situations where there were zero
21 African-Americans, or perhaps one or two,
22 zero Asian-Americans, or perhaps one or two.

1 Now, the differences in drugs and
2 devices is that for NDAs, the sponsors must
3 present a summary of safety and effectiveness
4 data by demographic subgroup.

5 And the IND holders must submit
6 annual reports with information about the
7 age, gender and race of subjects enrolled in
8 clinical studies. But there are no similar
9 requirements for medical devices. And we
10 think that's something that it's time to
11 really start looking at and using the
12 resources from MDUFMA as well as
13 appropriations to make sure that that's done.

14 Let's look at the NIH policy. The
15 NIH policy requires the inclusion of women
16 and minorities in all research involving
17 human subjects.

18 And the exception to the policy is
19 in situations where it would not work to
20 protect the health of the human subjects
21 because it would be unsafe, or if such
22 research is not needed. And we think this is

1 an excellent model for CDRH.

2 I'm going to talk a little bit
3 about cosmetic surgery. I think it's a
4 really good example, because we're talking
5 about devices and I'm talking about cosmetic
6 surgery involving devices such as -- wrinkle
7 fillers and breast implants are two good
8 examples where the product is not
9 life-saving.

10 So we're not dealing with something
11 that has to be rushed to market because
12 people's lives are at stake. And so for that
13 reason, we have to be particularly concerned
14 about the safety, short-term and long-term,
15 and the safety for all Americans, not just
16 white people who are already young and
17 healthy. In 2000, people of color accounted
18 for 14 percent of all cosmetic surgery
19 procedures in the country according to the
20 plastic surgeons. And in 2005, people of
21 color accounted for 20 percent of all
22 cosmetic surgery procedures, so it's on the

1 increase.

2 Unfortunately, many of these
3 wrinkle fillers and other cosmetic devices
4 are being approved without any useful
5 information about people of color. As I
6 said, the products are not life-saving, and
7 it is also important to note that these
8 products are often used off-label. So even
9 if they are safe for some groups or for some
10 procedures, they may be used for other groups
11 and other procedures.

12 We know that racial and ethnic
13 groups do respond differently to medical
14 treatments and devices, and of course FDA has
15 recently approved a prescription drug
16 specifically for African-Americans.

17 But let's look at how implants and
18 implanted medical devices might have a
19 different response. We know that
20 African-Americans are more likely to have
21 keloid/scarring. We know that in response to
22 laser treatments, there is hypo-pigmentation

1 risk. And we also know that
2 African-Americans are more susceptible to
3 autoimmune disease.

4 Keloid scarring can occur after an
5 incision, and it's is more likely for
6 African-Americans and Asian-Americans. And
7 here is two examples of keloid scarring: The
8 woman has a scar on her ear from having her
9 ear pierced, and it's a huge, like ball on
10 the bottom of her ear. It looks like an
11 earring, but it's actually her scar.

12 And the scar on that ankle is also
13 from a cut.

14 Here are some granulomas in the
15 mouth region -- it's not so clear, but you
16 can see this was a cosmetic injection, an
17 approved medical device, and there was a
18 reaction with these rather large granulomous
19 lumps over the lip.

20 This one was in the forehead where
21 there was necrosis and the skin died and left
22 that not very attractive appearance.

1 And as I mentioned, autoimmune
2 disease is of particular concern because
3 African-Americans are more at risk for
4 autoimmune disease, and implanted medical
5 devices, some may increase the risk of
6 autoimmune disease.

7 So for breast implants, there were
8 only a few, less than a dozen,
9 African-Americans and Asian-Americans in the
10 recent PMA for breast implants, even though
11 reconstruction with breast implants is
12 popular among African-American women and
13 augmentation with breast implants is very
14 popular among Asian-American women.

15 This is a sample photo for the
16 implant makers of what breasts are supposed
17 to look like after augmentation. And this is
18 what's called capsular contracture, where the
19 scar tissue hardens around the implant and
20 causes a distortion in the shape and can be
21 extremely hard and painful. Since we know
22 that there are racial differences in keloid

1 scarring, we do have to worry about scar
2 tissue development with implants.

3 MR. BARNETT: Two more minutes
4 please.

5 MS. ZUCKERMAN: This is a necrosis
6 after an implant. I just wanted to give an
7 example of Sculptra, a product that was
8 recently approved as a medical device for
9 HIV-AIDS patients but is now being widely
10 advertised for the horror and tragedy of
11 SmileLines for young women. So we need to
12 make sure that these products are safe for
13 everyone. And we need to make sure that the
14 post-market surveillance is also enough to
15 ensure the long-term safety for everyone.
16 And we know from experience and from the
17 report that FDA did that pre-market
18 agreements that require post-market
19 surveillance are not necessarily being
20 followed.

21 So we want to make sure it's safe
22 for everyone, again: Asian-Americans,

1 Hispanics, everybody. Elderly people. I
2 want to remind you that the National Academy
3 of Science's report found some problems with
4 medical devices surveillance for children.
5 And we want to make sure that these products
6 are safe for our kids.

7 The NAS recommended among other
8 things post-market studies be a condition of
9 approval, and that those post-market studies
10 follow children for a long enough time to
11 make sure that the product accounts for
12 children's growth and development, and to
13 make sure that there are annual reports on
14 that to make sure that when medical devices
15 are used for children, whether on-label or
16 off-label, that they're safe.

17 I want to end with a quote from
18 Dr. Jane Henney, former FDA commissioner:
19 "It's only through the participation of the
20 many populations that will ultimately receive
21 a new product that we can ensure that the
22 medical products we approve are appropriate,

1 safe and effective for all Americans and not
2 just a narrow cut of our country's
3 population."

4 Thanks very much.

5 MR. BARNETT: Thank you. Anyone on
6 the panel want to ask for clarification? If
7 not, I'd like to call a speaker who
8 registered today. She is Claudia Miller from
9 the University of Texas. Is she here? Okay,
10 come on up.

11 MS. MILLER: I'm a researcher, so I
12 guess I have a letter, handouts. I apologize
13 for that.

14 MR. BARNETT: Okay.

15 MS. MILLER: And I'll give you a
16 copy of my testimony as well.

17 Thank you for this opportunity to
18 talk about my views regarding improvements
19 that are needed to actually increase
20 safeguards for medical devices. I'm a
21 professor of environmental and occupational
22 medicine and a board-certified internist,

1 allergist and immunologist at the University
2 of Texas Health Science Center in San
3 Antonio.

4 For more than a decade, my research
5 has been focusing on people who report
6 developing chronic multisystem illnesses,
7 headaches, memory and concentration
8 difficulties, depression, fatigue, chronic GI
9 problems, fibromyalgia following an
10 identifiable exposure; for example, implants
11 in the body or to pesticides and solvents
12 used during remodeling, or chemicals used
13 during the first Gulf War.

14 I've served as a consultant to the
15 Department of Veterans' Affairs on the Gulf
16 War veterans' illnesses, the EPA on sick
17 buildings, including its own headquarters
18 building here in Washington, the National
19 Institute of Dental and Craniofacial Research
20 on temporomandibular joint implants, the
21 National Institute of Environmental Health
22 Sciences, the National Toxicology Program of

1 the governments of Canada, Germany, Sweden
2 and others.

3 What unites these seemingly diverse
4 groups, patients with implants, Gulf War
5 veterans and sick building occupants, is the
6 fact that following a well-defined exposure
7 event, a subset of individuals appears to
8 lose their prior innate tolerance, their
9 natural tolerance, for a wide variety of
10 structurally unrelated chemicals. I compare
11 to the way that diabetics lose their
12 tolerance for sugar; they lose their innate
13 tolerance for exposures.

14 Thereafter, everyday exposures,
15 including commonly eaten foods, medications,
16 alcoholic beverages, caffeine and chemical
17 inhalants such as fragrances, diesel exhaust
18 and tobacco smoke -- exposures that had never
19 bothered these people before and don't bother
20 most of us, but now they're triggering myriad
21 often disabling symptoms in these
22 individuals.

1 In environmental medicine, this
2 two-step disease process has come to be known
3 as Toxicant-Induced Loss Of Tolerance, or
4 TILT. It does not appear to matter whether
5 the exposure that initiated this process was
6 exogenous, like a chemical exposure to
7 pesticides, solvents; or endogenous such as
8 an implant. The body's response is
9 remarkable similar.

10 We've studied and reported on 87
11 people with surgical implants and I've given
12 you those papers. Three quarters of these
13 individuals had received breast implants.
14 Among the latter, 69 percent reported rupture
15 of an implant and 78 percent had one or more
16 implants removed. But these also include
17 other types of implanted devices, including
18 TMJ implants. Of those women who had
19 undergone explantation for breast implants,
20 almost half reported their health status as
21 greatly improved or somewhat improved.

22 Although we have not said all kinds

1 of implants, it appears that certain kinds
2 are more likely to cause this loss of
3 tolerance. Silicon gel breast implants, for
4 one, appear to cause these problems because
5 they tend to leak and rupture. TMJ implants
6 made of Teflon tend to cause similar problems
7 because the friction of the jaw joint, high
8 pressures cause the Teflon to flake off
9 basically inside the body.

10 And the fact that these are
11 long-term permanent implants often used by
12 relatively young patients means that
13 long-term research is especially important
14 before approval and post-market surveillance.

15 It's essential that MDUFMA ensure
16 adequate resources for long-term premarket
17 clinical trials and well-conducted
18 post-market surveillance. Using a validated
19 screening questionnaire which I've provided
20 to you, the quick environmental exposure and
21 sensitivity inventory, which is of very high
22 sensitivity and specificity and it's a

1 validating instrument to measure this problem
2 of chemical intolerance.

3 We found that the symptom severity
4 scores of implant recipients rival those of
5 environmentally exposed groups we were
6 studying, including Gulf War vets -- ill Gulf
7 War vets, I should add.

8 Compared to controls, implant
9 recipients also reported many more and more
10 severe adverse responses to everyday
11 environmental chemical exposures. Further,
12 implant recipients reported far more severe
13 reactions to a wide variety of foods,
14 medications, alcoholic beverages, caffeine
15 and other common exposures than did controls.
16 This is a new paradigm; we're not talking
17 about usually classified autoimmune diseases,
18 as have been studied in certain studies.
19 These are a much broader classification of
20 diseases, and this appears to be a new
21 paradigm for environmentally induced disease
22 that differs from classical toxicology and

1 allergy in important ways.

2 Toxicant-Induced Loss of Tolerance,
3 or TILT, for short, explains why infected
4 individuals may remain sick years after their
5 initial exposure. This is as a result of
6 subsequent triggering by everyday exposures
7 that they now have lost tolerance to.

8 Why do symptoms wax and wane in
9 such a bewildering fashion? Because
10 triggering exposures change over time in the
11 effects of these exposures, the symptoms
12 resulting from their exposures as they go
13 through the day overlap in time. Ironically,
14 affected individuals and their physicians may
15 be completely unaware of their intolerances
16 resulting from TILT because of a phenomenon
17 called masking. If people are reacting
18 adversely to multiple chemicals, foods,
19 drugs, and so on, and they are exposed to
20 these substances one after another during the
21 day, the symptoms resulting from these
22 exposures overlap in time.

1 Again, that's called masking. As a
2 consequence, there is so much background
3 noise that patients can't identify, nor can
4 their physicians, any specific triggers for
5 their symptoms. They just feel bad most of
6 the time, with chronic fatigue or flu-like
7 symptoms that won't go away.

8 Recent Canadian studies done at the
9 University of Toronto indicate that genetic
10 polymorphisms may underlie who is more
11 vulnerable to developing Toxicant-Induced
12 Loss Of Tolerance. At the same time, no one
13 is able to predict, and this is very
14 important, which individuals will be
15 affected.

16 In September, I chaired a meeting
17 on TILT sponsored by two NIH institutes:
18 NIEHS and National Institute of Alcohol Abuse
19 and Alcoholism. There is a report on that
20 meeting from a journal I've given you.

21 Invited scientists explored
22 clinical observations, animal models,

1 neuroimaging and genetic approaches for
2 understanding this emerging new disease
3 paradigm. The implications for you are
4 clear. To safeguard health, you must
5 determine which types of implants are more
6 likely to cause loss of tolerance, and the
7 time frame for problems.

8 If certain materials are more
9 likely to cause serious health risks, they
10 should not be approved unless benefits
11 outweigh the risks. The FDA must assure that
12 there are adequate warnings on the label so
13 that patients can avoid the health risks and
14 respond quickly to remove the implants that
15 are starting to cause symptoms.
16 Unfortunately, that may be too late in some
17 cases. And since removal of cosmetic
18 implanted devices such as breast implants are
19 not covered by health insurance, it is
20 especially crucial that they be held to a
21 high safety standard.

22 Unfortunately, women who become ill

1 from their implants may not be able to afford
2 surgical removal. Our research indicates
3 that a substantial proportion of implanted
4 women with TILT become so debilitated that
5 they are no longer able to earn a living, and
6 therefore unable to afford surgical removal
7 for many years unless they become eligible
8 for Medicare or Medicaid.

9 Some become so ill over time that
10 they are not able to tolerate hospitals or
11 surgery, even if they could otherwise afford
12 to have their implants removed.

13 Today's meeting is focused
14 principally on the device industry's
15 perspective, but as a clinician, I'm here to
16 encourage you to ensure long-term safety
17 standards and to take into account this more
18 susceptible subset of the population that may
19 have exposures to various devices.

20 We cannot predict ahead of time who
21 is going to have adverse effects until we
22 have more science. Thank you.

1 MR. BARNETT: Thank you. Anyone on
2 the panel want clarification on that? Okay,
3 now since this is the close of the last of
4 our six sessions, let me open the floor now
5 to questions from anyone about any of the
6 things you heard today; that is, any of the
7 six sessions. The only ground rule for this
8 one is that your comment apply to MDUFMA. So
9 let me do that. Anybody? You all talked
10 out? Okay, if that's the case, then let me
11 ask Linda if she wants to make a few closing
12 comments before we say goodbye.

13 MS. KAHAN: I just want to
14 reiterate Dan's appreciation for everybody
15 coming. I think that we did hear a lot of
16 good ideas, many of which focused on issues
17 that we ourselves of course have been
18 thinking about and that many of you have
19 brought to our attention before, and that
20 we're working on thinking about the right way
21 to go ahead, at the same time we're working
22 on meeting the current MDUFMA goals.

1 We look forward to working with all
2 of you over the next year so that we can
3 again get a program in place that's even
4 better than what we've got, so that we can
5 get safe and effective products to the
6 American public as quickly as possible.

7 Thank you very much for helping us.

8 MR. BARNETT: Thank you all.

9 (Whereupon, at approximately 2:24
10 p.m., the PROCEEDINGS were
11 adjourned.)

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