

TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CBER STAKEHOLDERS MEETING
COMMUNICATING WITH STAKEHOLDERS
FDAMA 406 (b)

Pages 1 thru 115

Washington, D.C.
August 14, 1998

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS AND EVALUATION RESEARCH

**CBER STAKEHOLDERS MEETING
COMMUNICATING WITH STAKEHOLDERS**

FDAMA 406 (b)

Friday, August 14, 1998

9:00 a.m.

Room 800
Hubert Humphrey Building
Washington, D.C.

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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P R O C E E D I N G S

Opening Remarks and Welcome

1 DR. ZOON: Good morning. First of all, I would
2 like to welcome everyone to CBER's 406(b) meeting. This is
3 the first of two meetings CBER is going to have for its
4 stakeholder. This is part of our response to the FDAMA
5 406(b) section, and we are delighted. I think the spirit of
6 openness and listening to the needs of our constituents is
7 very, very important for us. We will be having a sister
8 conference on the West Coast in two weeks, in Oakland. For
9 those of you who did not have the opportunity to attend this
10 one today, we hope that your colleagues will take the
11 opportunity to come to the West Coast and see us.

12 This is also a very difficult time, and I
13 appreciate everybody coming in the summer. I know this is
14 prime vacation time so I want to tell everyone thank you for
15 making the effort. I know many of you who were not planning
16 to attend rearranged your schedules and made time to come,
17 and I want to thank all of you for that.

18 I also would like to thank Gail Sherman, Dennis
19 Strickland, Pat Kuntza and our OCMA staff for all their help
20 and support for arranging this meeting today. It has been a
21 lot, a lot of work for our staff, on short notice, to put
22 this together and, as you can see, they have done a
23 wonderful job and I appreciate that very much.

1 There is a cafeteria in this building, when we
2 break for lunch, and there are bathrooms. I won't attest to
3 the quality of the food but you certainly take advantage of
4 that.

5 We are going to have three panels this morning and
6 early this afternoon. Each of you should have received a
7 packet when you came in. This includes a variety of
8 different pieces of information: an agenda, some information
9 on the Center for Biologics, as well as some statements that
10 have been prepared, and copies were available for those who
11 wished to do so.

12 We will also have, after each of our panels, an
13 opportunity for an open mike where people can make comments.
14 If, in fact, we move a little bit faster than the agenda
15 suggests, and if some of the individuals coming from
16 Massachusetts are here earlier, we may be actually be able
17 to finish a little bit earlier, but we will play that one as
18 we go along.

19 This activity, I believe, is something that we
20 have tried at various levels to reach out and talk to our
21 different constituents. This is really the first time that
22 we have opened it up to all constituents at the same time,
23 and I think it is very important, and I think it is
24 important for us to hear you. I also think it will help for
25 you to hear each other, and look at the different issues and

1 concerns that each of you has, and it will give us an
2 opportunity, at CBER, to present some of our initiatives,
3 some of our priorities and to get feedback from you on those
4 priorities.

5 For those of you that have not had a chance to
6 look at your packet yet, there is a docket for CBER for the
7 406(b). So, that docket will remain open, and we encourage
8 your input not only today but after the meeting. If issues
9 come up, we would be delighted to hear from you.

10 My first pleasure this morning is to introduce
11 Linda Suydam. Linda Suydam is the Associate Commissioner
12 for Strategic Management in FDA, and she will be giving an
13 FDA presentation on the stakeholders' meeting. So, thank
14 you. Linda?

15 **FDA Remarks**

16 MS. SUYDAM: Thank you, Kathy. Good morning, and
17 welcome. It is, indeed, a pleasure to welcome you to this
18 first of a series of stakeholders' meetings that the FDA is
19 having in the next few weeks in an attempt to meet the
20 requirements of Section 406(b).

21 [Slide]

22 FDA has consistently in the past I think looked
23 for and asked for input into our processes, but never in
24 such a formalized way as this. So, while Section 405(b)
25 mandates that we consult with the appropriate scientific and

1 academic experts, healthcare professionals, representatives
2 of patient and consumer advocacy groups and the regulated
3 industry, we feel that there is more than just that mandate
4 of 406(b). We want to have your input in understanding how
5 people view the agency in general, and how people view the
6 workload that we are facing in the next five to ten years.

7 We plan to issue the 406(b) plan, as is required
8 by law, on November 21st, and that will be the result of the
9 stakeholders' meetings that we have been having and will
10 have with our various constituents throughout the country in
11 the next few weeks.

12 This is a very intensive process. Perhaps we are
13 starting it a little late this year in terms of the process
14 and having to have this finished by November, but we want to
15 remind people that we see this as an iterative process.
16 This is something that we intend to do in the future, and
17 that we continue to get and ask for your feedback. It will,
18 hopefully, be as formalized as this but also will allow you
19 the opportunity to provide us with your input over the year
20 and the next few years.

21 - [Slide]

22 Section 406(b) asks us to look in our plan at six
23 objectives, and the objectives are those that we would like
24 you to focus on as you are providing us input. The first of
25 those objectives speaks to the kind of input and information

1 that the FDA provides to its constituents about the process
2 for review of applications and submissions. The second is
3 also an informational objective, and that is to maximize the
4 availability and clarity of information about new products
5 for both consumers and patients.

6 Both of those are obviously directives that we
7 believe are important, that we want to get as much input in
8 as possible, and that we want to continue to hear about from
9 you over the next few months.

10 [Slide]

11 The next two objectives are to implement
12 inspection and postmarket monitoring provisions of the Act,
13 and we are looking for input on how that can be done
14 creatively, effectively, and to meet the objectives of the
15 FDA as a consumer health protection agency.

16 We also want to ensure access to scientific and
17 technical expertise. That is why we continue to look for
18 input to our various processes and are hopeful that you will
19 give us new ways of maximizing that input over the next
20 year.

21 [Slide]

22 The final two objectives are to establish
23 mechanisms for meeting the established time periods for
24 review of applications and submissions by July. As you
25 know, FDA has statutory mandates, some of which we are

1 meeting and some of which we are not, and this objective is
2 to encourage us to establish, as part of the plan, how we
3 will meet those objectives. The final one is how we will
4 eliminate the backlog of applications and submissions by
5 January of the year 2000.

6 [Slide]

7 In addition to the FDAMA six objectives, we are
8 also interested in having your input into what we are
9 calling the six areas of concern, issues of concern that we
10 have. These are six areas that we are focusing on, and will
11 highlight in our 2000 budget to the Congress, and that we
12 think require us to look at in terms of how we are doing
13 this activity, can we do it more efficiently, and can we do
14 it in a way that we are not doing now. So, we are looking
15 for new ideas about adverse event and injury reporting.

16 As you know, there have been a number of articles
17 that have talked about the issue of adverse events with
18 prescription drugs, and we believe that is just the tip of
19 the iceberg in terms of all of the products that FDA
20 regulates.

21 The agency is also very concerned about product
22 safety assurance, and how we are meeting our obligations
23 under the law in terms of our inspectional and compliance
24 activities.

25 Product application review has been an area where

1 the agency has focused in the last few years, and where we
2 have made significant progress but where we continue to need
3 to make progress, and we want to be able to do that activity
4 in the most efficient way, meeting consumer needs as well as
5 the industry's concerns. We are looking for feedback on
6 that activity as well.

7 [Slide]

8 Then, the final four areas that we are focusing on
9 are the President's initiative on food safety, which I think
10 most of you have read about. Even though food is not the
11 area of concern today, it is one of the areas that we need
12 to focus on, all of us, and we are putting additional
13 resources into that activity.

14 We also want to focus on our outreach activities
15 and make sure that we are connecting with our various
16 constituents, and that is why this process is so important
17 to us.

18 We too believe that we are a scientific regulatory
19 agency and, as a result, we need to be very concerned about
20 the scientific infrastructure and the research activities of
21 this agency.

22 Finally, is the issue of tobacco. As you know,
23 the FDA has undertaken in the last few years a major
24 initiative in the area of eliminating the number of youths
25 who start smoking, and I think those efforts will continue

1 to be an important public health initiative.

2 We are asking that you continue to send us
3 information. The docket will be open for the next few
4 weeks. We would like to have your input into both the
5 Biologics specific docket but also to the FDA docket as
6 well.

7 [Slide]

8 We have three ways that you can comment. We
9 believe that the information that is available on the web
10 pages is something that can give you the kind of background
11 that you need. In addition, I would like to present some
12 FTE numbers so that you can see the kind of resources that
13 the FDA has had over the last few years and, in fact, why we
14 feel pressured in terms of the ability to be able to meet
15 our statutory obligations.

16 [Slide]

17 As you can see from the chart, the yellow, which
18 we are calling the "shrinking" FDA, shows you in constant
19 dollars what resources we have available for the basic
20 activities of the agency. While our budget has increased
21 significantly, if you look at it in terms of actual dollars
22 you will see that most of that increase is eaten up by
23 inflation, and also it is eaten up by the new programs that
24 are mandated and that have a specific dollar figure that is
25 mandated to those programs. As a result, the real dollars

1 that the agency has to do its ongoing work have been
2 decreasing over time. So, as a result, there is a
3 tremendous amount of pressure.

4 [Slide]

5 This chart shows that a little bit more. If you
6 look at it in terms of constant dollars with the increasing
7 workload, you will see that this erosion of FDA's base is
8 something that concerns us, and certainly puts an added
9 constraint on how we can do our work in the future.

10 So, that is why we are looking at asking each of
11 you to help us in figuring out what the important activities
12 of the agency are, and what the creative ways are that we
13 can go about in doing our job.

14 I am very happy to be here today, to be able to
15 have the input and listen to each of you during your
16 presentations, and I look forward to the next few weeks when
17 we have these meetings across all of the agency's
18 constituents. Thank you.

19 **CBER Remarks**

20 DR. ZOON: Thank you very much, Linda, for your
21 opening remarks.

22 I thought while we are gathered together I would
23 introduce a few people to you, and I would like to first
24 introduce a number of the members of our CBER management
25 team. If I could, I will start at the table. We have Dave

1 Feigal, who is the Deputy Director for Medical at CBER; Mark
2 Elengold, Deputy Director for Operations; Bill Egan, who is
3 the Deputy Director of the Office of Vaccines; Jerry Donlan,
4 who is the Deputy Director at the Compliance and Biologics
5 Quality. I will get to you; I have special words for you!
6 Becky Devine, who is the Associate for Policy; Don Peterson,
7 who is the head of our Office of Management; and Steve
8 Masiello, who is the head of the Office of Compliance and
9 Biologics Quality; and Mary Meyer, who is head of OCMA.
10 Thank you, Mary.

11 We also have some very special guests here. Part
12 of our initiatives would not be possible to accomplish
13 without the strong teamwork of CBER and our colleagues on
14 ORA. I would like to take special notice of Mr. Ron
15 Chesemore. Would you please stand up? Ron is the head of
16 ORA.

17 We also have two special guests. We have here
18 Elaine Cole, who is the District Director in Baltimore; and
19 Diana Kalitis, who is the Regional Northeast Director.

20 So, thank you all very much for coming. I think
21 this is a real effort among all of us to help and work
22 together to get the many tasks that we need done, and I
23 thought it would be nice for you to have an opportunity to
24 actually see the folks who are responsible for all these
25 activities.

1 [Slide]

2 What I would like to do in the next 20 minutes is
3 just give you a brief overview of some of the activities of
4 the Center for Biologic, and I would like to start out with
5 our mission statement. This is very important, and it was a
6 fundamental part of the FDA Modernization Act. Although
7 CBER very much concurred with the revised FDA statement, we
8 actually revised ours several years before to reflect very
9 much the spirit that was stated.

10 Our mission statement says that our mission is to
11 protect and enhance the public health through the regulation
12 of biological and related products including blood,
13 vaccines, and biological therapeutics according to statutory
14 authorities. The regulation of these products is founded on
15 science and law to ensure their purity, potency, safety,
16 efficacy and availability.

17 As all of you know, with the diversity of CBER's
18 products, this creates many challenges for us and we all
19 work together, both within CBER and ORA, and with the
20 industry and the consumer groups and others affected in
21 order to make sure that this actually happens.

22 [Slide]

23 This overhead actually displays the types of
24 products that we regulated. Those products are increasing
25 in their diversity over time because many of the new

1 technologies are being incorporated into CBER's portfolio.
2 These include our traditional products such as vaccines,
3 allergenic extracts, blood and blood components, blood
4 derivatives, and more recently tissues. But it also
5 includes a number of the new biotechnology-derived products
6 including monoclonal antibodies, recombinant DNA-derived
7 proteins, somatic cell and gene therapy and, more recently,
8 xenotransplantation.

9 These have been very important to CBER, and all
10 the products are important to our Center and we have to pay
11 attention to each of the types of classes. This, in some
12 ways, makes priority setting very challenging for CBER
13 because there are many different demands on our organization
14 and we strive to do all of these well.

15 [Slide]

16 We have had a number of successes in our Center,
17 and I would just like to quickly go over those, in the past
18 five years predominantly. These include the reinventing
19 government initiative. Many of you are aware of this
20 administrative initiative, and many changes have occurred in
21 CBER even prior to the FDA Modernization Act.

22 We have simplified manufacturing changes. We have
23 eliminated the ELA for specified biotech products, as well
24 as lot release for specified biotech products.

25 We have developed the harmonized application form

1 for both NDAs and BLAs.

2 As many of you have seen, we have been publishing
3 guidance documents on the chemistry, manufacturing and
4 control sections for all our products, and these will help
5 us prepare, as we are now, for the implementation of the new
6 provisions of the FDAMA.

7 We have made great progress on the proposed rule
8 for a single biologics license, as recently issued. Again,
9 we have worked very hard on a number of initiatives
10 regarding review of labeling and elimination of the pre-
11 approval labeling. We have also been very aggressive at
12 improving our IND oversight functions. So, that has been an
13 active area.

14 The prescription drug user fee program, as Ms.
15 Suydam mentioned, actually has been a very successful
16 experiment, and we are now in phase two of that experiment.
17 CBER has met all the goals, and in many cases has exceeded
18 all the goals of the prescription drug user fee program, and
19 we are very proud of our accomplishments in that area. As
20 you will see in the next few slides, that progress has not
21 been limited just to the user fee products. We have put
22 many of our management initiatives in place for our non-user
23 fee products, and have made great progress in the management
24 and time-lines of those particular product reviews.

25 We look forward to the PDUFA-II program. I think

1 we, at CBER, believe that we can interact with you at the
2 IND level and that is very important in getting products to
3 market sooner. I think that interaction of scientific and
4 regulatory staff in dealing with the complex issues of
5 biological products is absolutely critical to meet the
6 public's needs for these safe and effective medicines.

7 We have a strategic plan for our Center, and I
8 will discuss that with you. It has been very successful in
9 moving forward a number of initiatives which I will outline.

10 The international conference on harmonization has
11 been very, very successful. CBER has taken the lead on many
12 documents, in particular in the area of biotechnology and in
13 the quality and safety aspects, but also has had enormous
14 input into the efficacy region of those documents. We
15 believe the world is getting smaller and the efforts on
16 globalization are key to the success of the future of
17 getting products that are safe and effective to the American
18 public.

19 This also applies to the WHO activities, the World
20 Health Organization. Many of the products that are not
21 covered by ICH will be covered and harmonized using WHO as a
22 vehicle for harmonization, and we believe this will be very
23 important in the areas of blood and vaccines.

24 With respect to cellular and gene therapy, a great
25 deal of progress has been made in this field. CBER has

1 sponsored numerous conferences and workshops to assist this
2 developing technology, and I think has achieved a fair
3 amount of success in providing the guidance that is
4 necessary to move these initiatives forward.

5 Our research program has recently been the first
6 to have a major external review. Every program was looked
7 at by a body of 26 distinguished scientists from academia,
8 industry and government. This included six members of the
9 National Academy of Sciences. There was a great deal of
10 support for the research program and its importance to the
11 ability of CBER to do its work in regulating biological
12 products. So, as you can see, there has been a lot of
13 activity at the Center, and we are very proud of the
14 successes.

15 [Slide]

16 Just to show some data regarding this, if you look
17 at both our user fee and non-user fee approval times, you
18 can see that the processes, both the management processes
19 and the prescription drug user fee program, have had
20 enormous effect on the reduction in the time it takes to
21 approve safe and effective products.

22 [Slide]

23 This overhead shows the same data for supplements.
24 Our workload is actually increasing at CBER, and this is
25 indicated in the next overhead.

1 [Slide]

2 This shows you our IND workload. Since 1997 we
3 have actually seen an increase in both our biotech and non-
4 biotech INDs for this year, and I think this is very much
5 stimulated by some of the changes made at CBER, as well as
6 it is going to be fostered by the FDA Modernization Act.

7 [Slide]

8 This overhead describes the strategic goals of our
9 Center with respect to our strategic plan. We put this plan
10 into place in 1995, and have been actively working on it and
11 we have made much progress in each of these areas.

12 The first is a managed and integrated regulatory
13 program from discovery through postmarketing. We have
14 mapped out the entire business processes of our Center. We
15 put teams together. They identified weaknesses and
16 bottlenecks. They redesigned our business processes to
17 create solutions. We are now in the process of implementing
18 a newly designed, streamlined managed review process. The
19 first step is to roll out this process beyond the review of
20 license applications and to focus now on the investigational
21 new drug phase of our processes.

22 With respect to our research program, I talked
23 about our external review. We are currently considering the
24 comments of the external review and are preparing a number
25 of initiatives to respond to that in the Center. We are

1 also developing a coordinated model of research and I think
2 this is going to be very key in really honing in on our
3 expertise as scientists, researchers and the regulatory
4 process through our researcher, reviewer, and regulatory
5 scientist models.

6 A high quality and diverse work force is very
7 important. Our people are our most important asset, and to
8 do the job we need highly skilled individuals that are good
9 listeners and work well with others.

10 Interactive information systems which are integral
11 to all our processes has been a major initiative at our
12 Center. It has been reaffirmed in PDUFA-II. We have
13 dedicated an enormous amount of effort in this area. We
14 have achieved desktop standardization in our Center. We are
15 working very hard on electronic submissions, not only for
16 BLAs and NDAs but also for INDs. We are implementing a
17 docket management system, and our regulatory management
18 system is currently being developed so we have a single
19 corporate database for our entire center. We have also
20 implemented electronic lot release.

21 Leveraging resources is an important part of our
22 activities. We recognize that resources will continue to be
23 limiting. Developing strategic partnership to accomplish
24 our mission is key in CBER's initiatives.

25 [Slide]

1 Some of the major initiatives and action plans
2 that are currently under way include the implementation of
3 the FDA Modernization Act, the implementation of the
4 Prescription Drug User Act-II, and continuing our activities
5 on the international conference on harmonization,
6 particularly with respect to the initiatives on GMP for
7 active ingredients and pediatrics in a common technical
8 document.

9 Again, we are continuing to work on our strategic
10 plan, and completing the implementation of team biologics
11 which is a unique model of putting together product
12 specialists and trained, skilled investigators from the
13 field to act as a highly trained core team of individuals to
14 inspect biologics manufacturers. This also has an aspect of
15 streamlined processes within all forms of compliance, and I
16 think to date it has been a very successful initiative for
17 postmarketing inspections.

18 We have also engaged in a tissue regulatory
19 framework. Last February, in 1997, we published a
20 reinventing initiative on the regulation of human tissues.
21 This is a tiered risk-driven approach based on the
22 regulatory variables and concerns that one might have about
23 tissues, and we are currently in the process of preparing
24 proposed rules for this particular initiative.

25 The blood action plan is a major initiative in

1 CBER. We have accomplished a tremendous amount in this
2 area. You have seen guidances. You will see a number of
3 proposed rules being issued -- very important areas. I
4 think this will continue to be a major initiative over the
5 next two years. It includes updating our regs. and new
6 regs. It includes trying new approaches to the regulation
7 of biological blood products, particularly using a monograph
8 system.

9 We are also looking at emerging infectious
10 diseases, and making this a priority in our blood area to
11 make sure that we are as vigilant as we can be with respect
12 to our ability to identify and react to new infectious
13 diseases as they may affect blood and tissues.

14 The xenotransplantation action plan is a plan that
15 we put together at the Center to deal with the new
16 technology of xenotransplantation. This will include
17 xenotransplant patient regulations and guidelines. It will
18 affect the issues of disclosure in this very sensitive and
19 important area.

20 [Slide]

21 Some of our challenges for the future are to
22 successfully complete all that is on our plate, and this in
23 includes FDAMA, PDUFA-II, our international harmonization
24 efforts, being vigilant in the area of emerging infectious
25 diseases, including xenotransplantation and dealing with the

1 issue of human cloning and reproductive technologies.

2 [Slide]

3 Some of the funding challenges that we face are
4 many, unfortunately. These include funding initiatives for
5 tissues, xeno, blood, the implementation of the FDA
6 Modernization Act, the ICH processes, gene therapy, emerging
7 infectious diseases, bioterrorism and our research programs.
8 Those are the challenges that we are working very hard on at
9 the moment.

10 [Slide]

11 There have been a number of significant
12 legislations that have been passed that has impact on CBER's
13 daily activities. Those are listed on this slide. I am not
14 going to go through all of them. A number of them have been
15 mentioned already, but each of these impacts on our daily
16 work and our daily considerations. Many of these
17 initiatives have been unfunded. Clearly, the prescription
18 drug user fee program in its right was a funded initiative,
19 additive funds, for the review of new drugs and biologics.

20 [Slide]

21 In the last few minutes I would like to give you
22 the state where CBER is right now with respect to our
23 operating budget and FTEs. This shows you that in spite of
24 all the increasing responsibilities we have had our budge is
25 declining. This is actually well seen in this graph. Our

1 PDUFA dollars have actually increased. To a large extent,
2 this has been targeted for the review process, but also for
3 information management initiatives. This negatively
4 affected the research programs because of some of the
5 reductions in the ability to use the PDUFA dollars for
6 research, but has been very helpful in the information
7 technology area.

8 The biggest hit though is in our base funding. As
9 you can see, those dollars have decreased dramatically over
10 the past five years.

11 [Slide]

12 One of the hardest hit at CBER has been our
13 research budget, and this slide indicates the impact it has
14 had on CBER. Because of the new initiatives, it has been
15 increasingly stressful on the organization to maintain the
16 level of research dollars that have been fairly stable in
17 the early '90s.

18 [Slide]

19 This overhead shows you the FTEs. While the FTEs
20 have been fairly stable over the past four years, as you can
21 see, we actually, even with the re-initiation of the
22 prescription drug program, have had a decrease in the number
23 of FTEs allotted to the Center for Biologics.

24 [Slide]

25 The Modernization Act is very important to us. We

1 are committed to its implementation. This is just part of a
2 very large initiative that our Center is very happy to
3 participate in. We see this as a fundamental role of our
4 organization to serve the public, to serve our stakeholders,
5 and we appreciate the opportunity. We look forward to
6 hearing from you today, and your comments today, as well as
7 any comments you or your colleagues may have after today.

8 [Slide]

9 The docket number is listed on this slide, and
10 there are three ways to comment. One is by mail; one is by
11 email and, finally online.

12 I want to personally thank all of you for coming
13 today, and I very much look forward to hearing from you.

14 I would now like to ask our first two panelists to
15 please come up to the front. Alan Goldhammer will be the
16 first to present. Welcome, Alan.

17 **Panel A**

18 **Biotechnology Industry Organization**

19 DR. GOLDHAMMER: Thank you very much, Kathy, and I
20 would also like to thank you for adjusting the schedule. I
21 have another meeting that starts in about 25 minutes. So, I
22 will have to duck out shortly after my presentation here.

23 I am Alan Goldhammer, Executive Director for
24 Technical Affairs at the Biotechnology Industry
25 Organization. We welcome the opportunity to address the

1 questions that were recently posed by the FDA in its July
2 22nd message to the stakeholders.

3 In that message, FDA noted that its obligations
4 under Section 406(b) of FDAMA are to meet with interested
5 parties, with the goal of receiving input as to how the
6 agency can best meet its regulatory responsibilities. This
7 document was frank in its mention that innovations and
8 efficiencies alone may not be sufficient to deal with the
9 enormous growth in FDA's obligations that have been fueled
10 by rapid technological developments and increased complexity
11 of regulated products and mushrooming global trade. I think
12 you have already heard that from both Linda Suydam and Kathy
13 in their presentations this morning.

14 The agency goes on to identify a series of areas
15 that they believe are critical to the agency's public health
16 mission. The agency notes that although we have shared
17 areas where we have real concerns about our ability to meet
18 our statutory obligations, our stakeholders can be assured
19 that we are embarking on this consultation process with no
20 preconceived conclusions, and the agency sets forth again
21 the seven questions designed to assist in developing a plan
22 for complying with FDAMA and these are the issues that are
23 before us today.

24 Before I address the specific points, I would like
25 to note the interconnecting thread that is implicit with

1 FDA's message to the stakeholders, as well as the questions
2 that were posed. This theme, in our mind, is the need for
3 adequate resources and I think you have just seen some
4 dramatic view-graphs documenting this.

5 Six years ago, the Prescription Drug User Fee Act
6 was passed in response to a specific crisis that there were
7 insufficient resources within the FDA to review drugs and
8 biologics. The agency was not able to meet its obligation
9 in reviewing drugs and biologics in a timely manner. The
10 backlog of applications was growing out of control, and a
11 convincing case could and was made for the need to augment
12 the agency's resources in a targeted manner, accompanied
13 with performance goals so that new priority products could
14 be reviewed and acted upon in six months, standard
15 applications in 12 months.

16 The success of this program was self-evident, and
17 one of the critical sections of FDAMA was the
18 reauthorization of PDUFA with a new set of goals for an
19 additional five years. Our thoughts are that the
20 performance enhancements can shorten drug development by
21 anywhere from 10-15 months.

22 The success of PDUFA should not be taken as a sign
23 that the regulated industry only needs to give money to FDA
24 and that all the problems will be solved. Our industry is
25 not FDA's only constituent. Healthcare professionals,

1 patients who rely on new medical technologies, and the
2 general public all have a vested stake in an FDA that is
3 fully funded so that it might carry out its responsibilities
4 for all the publics that it serves.

5 This means that FDA must have adequate
6 appropriated congressional funding. It has been our
7 experience that user fees can best be used to address
8 certain narrow programmatic problems. However, the public
9 constituencies' overall interests about FDA's ability to
10 carry out its functions must continue to be addressed via
11 the appropriations process. There is no question that
12 recent efforts by both the administration and Congress to
13 see a balanced budget have had an impact on FDA's operating
14 budget. Senior management at FDA must be prepared to
15 present its budgetary needs to both OMB and Congress in a
16 realistic and forceful manner.

17 We would offer specific responses to three of the
18 seven questions, and these will be submitted in greater
19 length to the docket prior to its close.

20 On question one regarding FDA's explanation of the
21 submission review process, we have two comments. Our
22 industry has spent considerable resources trying to make the
23 drug development process more predictable. FDAMA clarifies
24 many FDA responsibilities regarding its role in approving
25 the predictability of drug development. However, FDA's

1 increasing reliance on advisory committees both to answer
2 general questions about products during the development
3 process, and to review information as the penultimate step
4 prior to licensure, is oftentimes unpredictable. Outcomes
5 of advisory committee decisions often surprise both the
6 sponsors and the FDA.

7 There appear to be different internal practices
8 between different centers regarding the use of advisory
9 committees. We believe it would be useful for the agency to
10 have a mechanism by which it can receive sound advice on
11 scientific questions. The advisory committees are an
12 appropriate vehicle here. However, it may be appropriate to
13 convene a working group from the regulated industries to
14 review present agency use of advisory panels and make
15 recommendations as to how the process might be improved to
16 maximize their utility to the FDA. We will be submitting
17 some more thoughts on this to the docket.

18 The second point is that oftentimes agency actions
19 highlight an outdated or vague regulation or guidance that
20 is in need of revision. In such cases, these should be
21 identified as early as possible, and the FDA should reach
22 out to stakeholders for discussion of these issues.

23 An example of this are definitions of the same
24 versus different for orphan drugs. This has particular
25 application for the biotechnology industry because chemical

1 structures or monoclonal antibodies and recombinant proteins
2 are very complicated and sometimes fall into grey areas as
3 to whether they are the same or whether they are different.
4 If a product is not the same, then it can receive a separate
5 orphan drug designation. However, if not, then clinical
6 superiority or reduction in adverse reactions must be
7 demonstrated. Would demonstration of a major improvement in
8 patient care, that is, combination of such factors as higher
9 effective dose or ease of administration qualify under this
10 provision? It would be useful to consider developing a
11 guidance document or revising the regulation to address
12 these issues.

13 The second question that we would like to address
14 is assuring product quality and safety. The issue of
15 product quality and safety is one that is never compromised
16 within our industry. Our products are mostly large
17 molecular weight proteins. The manufacturing processes and
18 purification procedures are complex. Much time and effort
19 is spent during the development process, as well as FDA's
20 review of the license application, to design manufacturing
21 process controls and a quality assurance process and program
22 that will lead to a final product of the highest possible
23 quality and consistency. We would also note that FDA has in
24 place regulations that the reporting of adverse reactions,
25 another area that they have identified as a critical issue.

1 One of the key agreements reached during the
2 renegotiation of the Prescription Drug User Fee Act 18
3 months ago was to provide FDA with extra funding to move it
4 towards a fully electronic filing environment over the next
5 five years. One of the areas noted which would fall in to
6 this area was adverse event reporting. This should
7 streamline reporting and data analysis, and we are prepared
8 to work with FDA and other stakeholders on this matter as
9 issues are identified.

10 The third major point that I would like to
11 address, and one which is very important and is identified
12 as a priority of our board is that of the FDA science
13 infrastructure. We believe that there needs to be a
14 continuing strong commitment within the Food and Drug
15 Administration towards maintaining an appropriate scientific
16 base. Regulatory decisions, including the development of
17 guidance documents and regulations, must be made on the best
18 available science. It has been the experience of our member
19 companies, with numerous examples relating to both clinical
20 development and complex manufacturing issues, that these
21 were speedily resolved because of the scientific expertise
22 within the Center for Biologics. The recent FDA science
23 board review of CBER activities was positive in this regard.
24 There needs to be a closer tie with industry in identifying
25 research areas and reviewing ongoing programs, and I think

1 we can work towards this goal. Our board of directors has
2 identified this as another major priority. We are carefully
3 examining this issue and expect to file specific comments on
4 the docket.

5 Thank you.

6 DR. ZOON: Thank you very much, Alan. Are there
7 any questions? Since Alan has to go, I will take the
8 opportunity to ask if there are any clarifications or
9 questions? No? Thank you very much.

10 DR. GOLDHAMMER: Thank you.

11 DR. ZOON: I would now like to introduce Bert
12 Spilker. He is senior vice president, science and
13 regulatory affairs of PhRMA.

14 **Pharmaceutical Research and Manufacturers of America**

15 DR. SPILKER: Thank you, Kathy.

16 Good morning, members of CBER, ladies and
17 gentlemen. I am Dr. Bert Spilker, senior VP of
18 Pharmaceutical Research and Manufacturers of America. My
19 comments this morning must of necessity be condensed in
20 order to fit the allotted time. Further details and
21 substantiation will be submitted to the docket.

22 PhRMA appreciates the opportunity to provide input
23 as FDA considers how best to achieve compliance with the
24 agency's various statutory obligations. It is important to
25 underscore, however, that consultation with stakeholders

1 like PhRMA does not relieve FDA from the ultimate
2 responsibility to manage and, as necessary, reallocate its
3 resources to achieve the statutory time-lines and other
4 goals of the FD&C Act in a timely manner.

5 I will address the questions in order. Question
6 one on agency explanations: We wish to make three points.
7 The first point is that it is important for FDA to make its
8 procedures more transparent, particularly in terms of good
9 review practices, also known as GRPs.

10 The second point, copies of GRPs, as well as CBER
11 and CDER reviewer handbooks plus MAPPS, which are mainly
12 CDER, for NDA and IND reviews should be provided to the
13 industry and other stakeholders even though these documents
14 may still be in draft form. This step would provide
15 industry with a better understanding of how these groups
16 operate, and also enable industry to bring out procedures
17 into conformity with FDA. This action is intended in the
18 spirit of openness to foster improved collaboration. This
19 action is also part of Section 119 of FDAMA.

20 The third point, allow more time for companies to
21 respond to FDA proposed labeling changes near the end of the
22 review period. At present, companies often have less than
23 24 hours to decide whether or not to accept FDA changes or
24 get an approvable letter with FDA language that is not in
25 the company's interest.

1 Second question on clarity of information: We
2 wish to make two points. First, we appreciate that FDA is
3 putting information about new drugs on the Internet. This
4 is extremely positive. This practice should be followed for
5 all products at the time of approval.

6 Second point, the FDA should allow companies and
7 other groups to provide well documented information on
8 marketed drugs using market forces.

9 On the third question we wish to make five points.
10 The first, there is nothing that is more important to the
11 pharmaceutical industry than the safety of our products.
12 Every day, worldwide, our companies are monitoring the
13 safety of their products. We have extensive systems in
14 place today to collect safety data and we report to the FDA
15 all adverse reactions according to regulations.

16 The second point, the FDA should stress to
17 Congress, the press and the public that the current safety
18 standards for new drug approval are significantly higher
19 than they were in the past. For example, in 1980 there were
20 an average of 1500 patients studied in 34 clinical trials in
21 the average NDA. These numbers have risen to over 4000
22 patients in 68 clinical trials today. The amount of safety
23 data is related to the number of patients exposed to a new
24 drug.

25 Third point, we support the views of 21 patient

1 organizations who wrote to USA Today last week to emphasize,
2 and I quote, "the FDA has not compromised its world-class
3 standards for the safety and effectiveness of new
4 medicines." Another quote is, "fear that in overreaction to
5 a small number of recent drug withdrawals, policy makers may
6 decide to slow down the drug approval process. This would
7 hurt public health and harm the patients we represent by
8 denying them the new treatments and cures they are so
9 anxious to receive."

10 The fourth point we wish to make is that both FDA
11 and the pharmaceutical industry must educate Congress, the
12 press and the public about the vast amount of safety
13 activities already in place. Recent drug withdrawals
14 demonstrate that the systems are basically working, not that
15 they are broken.

16 The last point, to the extent that the system for
17 monitoring the safety of medicines after they are on the
18 market can be improved, the pharmaceutical industry s eager
19 to work with the FDA, with patients, with doctors,
20 pharmacists, hospitals, Congress, and anyone else to achieve
21 that goal.

22 The fourth question is on FDA access to scientific
23 and technical expertise, and we wish to make six points.

24 First, we support FDA conducting targeted research
25 on regulatory policy, particularly if planned

1 collaboratively with industry.

2 Two, we support in-service training that supports
3 the skills of staff to conduct reviews of marketing
4 applications.

5 Three, we support training of field staff, partly
6 within pharmaceutical companies.

7 Four, we support increased collaboration with
8 other regulatory agencies worldwide. That is, collaboration
9 of CBER with other regulatory agencies worldwide.

10 Fifth, we support the establishment of periodic
11 meetings for division directors in both CBER and CDER with
12 up to four industry representatives on a bimonthly or
13 quarterly basis. The purpose of these sort of informal
14 meetings is to share scientific and technical information,
15 management ideas, overall approaches, and creative thinking.

16 Six, we support increased efficiency in the use of
17 current resources within CBER.

18 Question five is on review of non-user fee
19 products. The point we want to make is that the current
20 level of full-time support staff paid through user fees
21 should not be diminished.

22 Question six is on ideas to eliminate backlogs.
23 Here, our comments will be made to the docket only.

24 The last question is on other objectives beyond
25 the six. Here, we wish to make three additional comments.

1 First, it would be valuable for reviewers to have
2 brief sabbaticals in the regulated industries. This will
3 increase their knowledge of the industry, its procedures and
4 its perspectives. Thus, they will better understand the
5 industry they are regulating. It should be noted that CDER
6 chemists currently have such sabbaticals in place.

7 Second point, the agency should educate the public
8 about benefit-to-risk ratios and the fact that medical
9 interventions such as surgery, medicines, devices, and even
10 diagnostics and foods are not totally without risks.

11 The last point, there is a need for external
12 advisory panels to advise FDA on efficient administrative
13 policies and activities.

14 Thank you for the opportunity afforded me to
15 address you this morning.

16 DR. ZON: Thank you very much. This statement is
17 now open for questions by any of the panel members.

18 MS. SUYDAM: Dr. Spilker, I have a question about
19 making agency's procedures more transparent. You had,
20 obviously, one suggestion which is that we provide reviewer
21 handbooks. Are there other things that you think we should
22 be doing that we are not doing?

23 DR. SPILKER: One other point that was mentioned
24 today was to initiate meetings on a periodic basis between
25 division directors and industry representatives. We are not

1 talking about the sessions that currently take place
2 sometimes every five years and sometimes eight years.
3 Recently one director said he felt that every eight years
4 was more than enough.

5 [Laughter]

6 But those are more formal and larger meetings. We
7 are talking about more informal ones, not to talk about
8 specific drugs or anything but just policies, ideas, ways of
9 working together more collaboratively and better. I think
10 that Alan Goldhammer mentioned something about getting
11 together with industry ahead of time to talk about
12 guidances. That, in a sense, may not just be making what
13 you do more transparent but I think the key word from
14 industry's perspective is that we would like to collaborate
15 as much as possible. We recognize that you will make
16 decisions but at least you will have input. I think that
17 there are some examples, which I will be discussing on
18 Monday, of some guidances that were issued without industry
19 input and led to a number, from our point of view, problems
20 which had to be addressed. I think we can forestall these
21 and prevent these by having more meetings ahead of time,
22 such as the types of meetings that I have mentioned and
23 others that you are aware of.

24 MS. SUYDAM: Thank you.

25 MR. ELEGOLD: I would like to follow up on

1 Linda's question. In these, which you described as small,
2 informal meetings with four representatives, what occurs to
3 me, in my mind, in how to implement that -- have you
4 considered what the impact of the Federal Advisory Committee
5 Act would be on our implementing that? That is the first
6 thought that crosses my mind. Once we seek advice on
7 guidances, we pretty much are locked into making it an open
8 public meeting, which tends to be large.

9 DR. SPILKER: Thank you for asking that. Those
10 are really two separate issues totally in my mind. What I
11 was talking about was meetings with division directors and
12 it was not to be talking about guidances at all but just
13 ways in which industry interacts with the division
14 directors. For the guidances I quite understand your point.

15 MR. ELENGOLD: I think though even in ways of
16 doing business that could be construed as seeking advice
17 and, at least in my mind, would trigger a need to get some
18 kind of legal opinion on whether that would constitute
19 advice seeking. You yourself said giving advice on how to
20 better handle things. Once you go to more than one
21 organization or group it may trigger that.

22 DR. SPILKER: Well, I think this could be explored
23 though.

24 MR. ELENGOLD: We can explore it but, you know,
25 you should be thinking along those lines as well.

1 DR. SPILKER: Fair enough.

2 DR. FEIGAL: I have a question or maybe it is more
3 of a comment because I am not sure it is answerable, but one
4 of the phenomena that sort of interested many of us was
5 seeing the steady increase over the first five years of the
6 user fee of the number of new molecular entities coming in
7 or the number of supplements. One of the speculations, and
8 it relates to some of your comments about withdrawals, was
9 that the shortened review time and the more predictable part
10 of the process, the fact that there was also a shift towards
11 more first cycle approvals, had actually changed the
12 economics of drug approval and had actually made some things
13 which in the past would have taken so long to approve that
14 they wouldn't have been pursued, and the issue is where are
15 all these extra products coming from, and were these, in
16 fact, innovations or were we scraping the bottom of the
17 barrel, so to speak, of things that were sort of marginal
18 either for economic reasons or other reasons?

19 I was just wondering whether you have any thoughts
20 on the more rapid review time. Initially, when you look at
21 an improvement of 10-15 months, that is not all that
22 impressive although you realize how much work that is, to do
23 that. But are these things all related to each other, and
24 do you have any comments on those sorts of musings?

25 DR. SPILKER: Those are excellent points. The

1 first point I do want to take slight exception to, that
2 improvement of 10-15 months is not that great.
3 Proportionally, if you think of drug development as 10-15
4 years, which I think is still fairly accurate, I would tend
5 to agree proportionally. If you think about the about the
6 patent life of a drug, and also you think about the revenues
7 that a drug will bring to a pharmaceutical or biotechnology
8 company, I think that 10-15 days would be deemed very
9 important, and I guarantee you that that is the mind set
10 inside these companies and they will do anything within
11 their power to gain an additional 10-15 days, let alone
12 months. That wasn't the main question but I did want to
13 make that comment.

14 It is difficult for me to answer without doing a
15 total survey of the industry which, to my knowledge, has not
16 been done. I think what I would suggest the agency could do
17 to answer that question is to see how many INDs there were
18 in the pipeline beforehand. You may have had a lot of INDs
19 in the pipeline so that a lot of supplements and NDAs, PLAs,
20 BLAs etc. were submitted afterwards to make up the numbers
21 but the impetus was really growing.

22 I can tell you from personal experience at
23 Burroughs-Wellcome where I spent 14 years that in the
24 antiviral area, talking about Zovirax in particular of
25 acyclovir, that the very first application we had was for an

1 ophthalmic. We held that to put in an IV form. We then had
2 one for herpes encephalitis, and we were told by the agency,
3 during the '80s, that they would only review one antiviral
4 from the company at a time, and they were very nice to ask
5 us which one we wanted them to review. So, we had multiple
6 dosage forms, most of which were sitting on the shelf inside
7 the company and were not submitted to the agency. When we
8 asked questions, we said you have taken literally six years;
9 we have not had an approval on herpes encephalitis; why is
10 that? And, the answer came back it is the state-of-the-art
11 to use the drug; it would be malpractice not to use it. We
12 don't need to approve it right now since we are working on
13 others -- all of which was true because Vira A, or it could
14 have been C, was the only other drug available, which is not
15 nearly as good.

16 So, the point was that there were cases that I can
17 attest to where we were holding back these, and they were
18 sitting on the shelf. I don't know it that was true for
19 other companies or how widely spread that was.

20 DR. FEIGAL: I particularly appreciate hearing
21 CDER examples.

22 [Laughter]

23 DR. ZOON: I have clarifications, if I could.

24 DR. SPILKER: Certainly.

25 DR. ZOON: The first is when you stated you

1 support increased collaboration with other regulatory
2 agencies worldwide for CBER, did you have any specific in
3 mind because there are a lot of regulatory agencies out
4 there and I don't think we could do all of them?

5 DR. SPILKER: No, not at all. I would say that we
6 will be talking to the companies more and I can try to get
7 any clarifications and submit that information to the
8 docket.

9 DR. ZOON: That would be very helpful because we
10 want to hear from you where you think the issues are, and we
11 can certainly take that under advisement in our
12 consideration.

13 The second is that you said there is a need for an
14 external advisory panel to advise FDA on efficient
15 administrative policies and activities, and I was wondering
16 if you could just talk a little bit about what you think
17 this advisory panel should look like and the activities
18 which it should undertake.

19 DR. SPILKER: I can speak more to the second
20 point, and this was a result, as you can imagine, of some
21 brainstorming within different groups of the industry
22 representatives. The key word here is administration. We
23 are not talking about science. We may not even necessarily
24 be talking about reviews. But we do have a large
25 organization, although it is all relative of course, and

1 there are many administrative questions that come up
2 especially as you change, you grow, you move into different
3 areas with different responsibilities. We feel that a
4 modern management consulting type of approach, whether it
5 was one organization to turn to or a group of management
6 consultants who were independent, might advise you on ways
7 to structure some of the administrative changes that you are
8 considering. There were no specifics given except that in
9 general, and this again, I stress, was more of your internal
10 management and not to tell you anything but a group for you
11 to turn to, and it is certainly not going to be industry
12 people. They would be independent people who would be your
13 own advisors.

14 DR. ZOON: Okay, thank you. That is very helpful.
15 The other question I have for you is that on your first
16 point in question one you said you supported FDA doing
17 targeted research. Does this include the scientific
18 infrastructure of the organization?

19 DR. SPILKER: We were mainly focusing on the part
20 that you didn't read, which has to do with research on
21 regulatory policies. One good example, which we have
22 already spoken about when we visited with you, was the topic
23 of bovine spongiform encephalitis, or BSE, and the European
24 initiative that is still on the books for January 1, '99,
25 new products containing bovine products can be imported into

1 Europe, which includes gelatin in all capsules. So, you can
2 imagine the implications that this has for the
3 pharmaceutical industry, and there are questions of variance
4 of Jakob-Creutzfeldt disease in these products, etc. -- not
5 to get into the science, but this is indicative of the area
6 that we place the highest priority on, and I would like to
7 answer it and say that our priorities in terms of research
8 focus primarily on issues such as those where we see a great
9 need and you, at CBER and FDA in general, are in a much
10 better position I think than the industry is to conduct that
11 research and to have some impact on a very important issue.

12 DR. ZON: Thank you. The last clarification is
13 in your question seven, other objectives You listed that
14 reviewers from CDER have been on brief sabbaticals in the
15 regulated industry. I would just like to ask what
16 precautions are taken in order to prevent conflict of
17 interest?

18 DR. SPILKER: A very relevant question, and that
19 goes both ways of course. I think that that is a question
20 that can be best addressed by speaking with the appropriate
21 people within CDER and seeing also whether they think it is
22 a successful program. If you feel that it does have
23 applicability, we are raising this as something for your
24 consideration and saying that if you find that it does have
25 merit, then we would be open to discussing ways in which it

1 could be implemented. But that would only be if you felt
2 that it was appropriate.

3 DR. ZOON: Thank you very much. That is very
4 helpful.

5 MR. ELENGOLD: I have one more. In this
6 relatively brief statement, there are two points in here
7 where you allude to further quicker disclosures of
8 information -- the posting of approval information and
9 reviewed immediately and the wider dissemination of internal
10 procedures. To me, both of those in today's modern age
11 relate to putting stuff up on the Internet very fast. One
12 of the challenges that I know we, in CBER, have faced
13 repeatedly is the matter of priority and competing for both
14 general resources and ADP resources in particular, we have
15 to make some choices. Since it applies here in two places,
16 does the industry believe that this is a high enough
17 priority that it does deserve specific funding and, in fact,
18 specific funding of Internet initiatives for dissemination
19 of this under PDUFA?

20 DR. SPILKER: Thank you, Mark. The two, in my
21 mind, are very different. The putting of some information
22 on the Internet, which I did specifically refer to although
23 whether I mentioned the name Internet or not I am not sure,
24 is for a new drug at the time of approval. That, I don't
25 believe, would require additional resources. It was done

1 with Viagra; it was done with a couple of others. But if
2 you feel there are other ways -- you could put it in the
3 Federal Register and we can wait.

4 The other issue of the reviewer handbooks, GRPs,
5 etc., etc., I would suggest not putting those on the
6 Internet and just making them available in hard copy. If
7 you were to sell those at X dollars per copy to cover all
8 costs, we would be delighted to pay that and even some
9 administrative fees in there too.

10 Really, I am a pretty old fashioned guy when it
11 comes to documents, and anything I see on my screen I have
12 to printout anyway to read. I don't know if you are like me
13 but I certainly think that we are not asking -- and I am
14 really serious -- we are not asking for that to be on the
15 Internet.

16 MR. ELENGOLD: There are two issues on that. For
17 the posting of approval immediately, and other than saying
18 it is approved and the press release, that is an extremely
19 resource-intensive initiative. Faced with a 150-plus
20 review, getting it electronically converted, and redacting
21 it if appropriate to remove manufacturing methods is both an
22 ADP and technical/scientific intensive resource. And, that
23 has been a problem that we have faced and are facing right
24 now.

25 The second problem, no matter how technologically

1 phobic one is, is that under the Electronic Freedom of
2 Information Act Amendments, as soon as we make a document
3 available in hard copy any person -- and I see Mr. Weitzman
4 here, and he would be the first to immediately insist that
5 we make it available in electronic form at the same time in
6 a format that is usable.

7 So, they are completely intertwined and I can tell
8 you specifically that the CBER SOPP manual is not available
9 and posted on our Internet site specifically because of a
10 resource issue. So, they are intertwined whether we like it
11 or not.

12 DR. SPILKER: Let me clarify our position a little
13 further then. Of the two issues, the one that is much more
14 important to the industry is the second one, that of having
15 some understanding of GRPs, the reviewer handbooks etc. The
16 other one is not nearly as important and, in fact, we can
17 almost dispense with it. I do see, since we are talking
18 about speed there, that it is a question of the Internet
19 resources etc. I would hope that you could talk to your
20 attorneys within FDA to see if there is any way in which
21 these could be made available in hard copy, even charging
22 for them, and not for the electronic version. Possibly you
23 could just charge a lot more for an electronic version,
24 which might cover it, or just perhaps -- we shouldn't get
25 into it any further.

1 DR. ZOON: No.

2 MR. ELENGOLD: No, I don't want to get into
3 details.

4 DR. SPILKER: Let me just leave it there. I hope
5 I have at least clarified our position on that.

6 DR. ZOON: Thank you. Are there any other
7 questions? A question from the audience? Mr. Chesemore, if
8 you would use the microphone, please?

9 DR. CHESEMORE: Dr. Spilker, you mentioned under
10 question four that you support training of field staff
11 partly within pharmaceutical companies. This is an area
12 that I think many of us in the agency support, but when we
13 bring it up sometimes in other products regulated by FDA,
14 not just pharmaceuticals, some people feel that it is
15 inappropriate for the agency to participate in training with
16 the industry, and I just wondered if you could expand on
17 that a little.

18 DR. SPILKER: Yes, if it is deemed inappropriate
19 for field staff to be trained within the industry, then I
20 would like to see as a fall back, if that is considered
21 unacceptable, that industry has an opportunity to try to
22 present its viewpoints and its perspectives to the field
23 staff. I think one of the major issues that does exist
24 today is when field staff, and I think it is also true
25 within the agency, here in the District, but let's just talk

1 about field staff for the moment but I don't want to exclude
2 it, do not have a good understanding of what the regulated
3 industry is that they are dealing with. I think that the
4 industry should have, even if it is at a separate site, not
5 within the industry, an opportunity to just present its
6 views because there are occasions when inspectors come to a
7 company when it is quite clear that their understanding of
8 industry's perspective or their understanding of how
9 industry operates, its goals, etc., are not really fully
10 understood. I think having such an opportunity would
11 benefit both sides because really the goal of this entire
12 exercise is understanding so that both sides can do their
13 job. In this case, the field staff can do their job more
14 effectively for the agency.

15 DR. ZOON: Thank you very much. Are there any
16 other questions, clarifications? If not, I want to thank
17 you, Bert, very much for your comments and answering the
18 myriad of questions, and we will take a 15-minute break.
19 Thank you.

20 [Brief recess]

21 DR. ZOON: Let me ask the next panelists to please
22 come up to the table. We are now starting our next panel,
23 and this panel primarily is going to be focusing on blood
24 and related products.

25 I would like to introduce Mary Gustafson, from

1 CBER, who is head of the Division of Blood Applications, who
2 is here from the Office of Blood Research and Review to
3 clarify any issue that may be raised from that group.

4 I would like to first ask Roger Brinser, who is
5 representing the Coalition for Regulatory Reform, to please
6 make his comments. Thank you.

7 **Panel B**

8 **Coalition for Regulatory Reform**

9 MR. BRINSER: Thank you, Dr. Zoon.

10 Good morning. My name is Roger Brinser. I am the
11 Director of Regulatory Affairs for Sera-Tec Biologicals, LP,
12 a source plasma collection company. Today I am speaking to
13 you as a co-chair for the Coalition for Regulatory Reform.

14 CFRR was formed in 1994, at the request of FDA, to
15 bring the blood and plasma industries together to jointly
16 explore ideas for a more efficient regulatory system for
17 blood and plasma products. The CFRR is composed of the
18 American Association of Blood Banks, which includes the
19 American Red Cross and the Armed Services Blood Program
20 Office, America's Blood Centers, and the American Blood
21 Resources Association. This organization represents the
22 entire spectrum of blood and plasma collection and
23 transfusion interests. We appreciate the opportunity to
24 comment on the important topics outlined in Section 406(b)
25 of the Food and Drug Administration Modernization Act.

1 Agency communication -- recently, FDA's
2 communication with industry has improved greatly. The
3 agency has published proposed rules in a timely fashion,
4 given industry an adequate opportunity to comment,
5 disseminated draft guidance early in the process, and
6 conducted more frequent agency workshops to address
7 important regulatory changes. CFRR applauds FDA's improved
8 communication and encourages further steps in this regard.
9 Foremost, CFRR encourages FDA to strictly adhere to its good
10 guidance practices document and broaden the document's scope
11 of application. The greatest effect in terms of regulatory
12 efficiency is seen when industry is given an opportunity to
13 meaningfully participate in the regulatory process. Groups
14 like CFRR and others stand ready to work with FDA in
15 developing even initial drafts of agency guidelines.

16 Improve the review process -- in the last year the
17 Center for Biologics Evaluation and Research has made great
18 strides toward improving the licensure process. The
19 proposed rule to replace the product license application and
20 establishment license application, of PLA/ELA, has been
21 published and the biologics license application, of BLA,
22 process shows great promise. The guidance document that
23 implements the BLA, the so-called CMC guidance, also was
24 recently published. CFRR strongly encourages CBER to ensure
25 that the paperwork reduction and regulatory efficiency goals

1 of the BLA are maximized with its implementation.

2 In addition, FDA has a host of new tools for
3 effecting modifications or changes to approved applications.
4 These include the prior approval supplements, or PAS, the
5 changes being effected, or CBE30, and annual report
6 submissions. These are important milestones. However, much
7 work remains to be done in the area of biologics
8 applications. FDA should utilize these tools to the
9 greatest possible extent. The onerous PAS process should be
10 used only for novel products or for a first-time request to
11 license an establishment or product.

12 Areas where the agency has promised guidance and
13 which industry desperately needs, include guidance specific
14 to blood and plasma for CBE30 and, in particular, annual
15 reports and comparability protocols. These are tools that
16 may yield the greatest regulatory efficiencies but remain
17 untapped. Many companies already have been required to
18 submit annual reports without clear guidance on what the
19 reports are supposed to contain, or how the agency will use
20 this information.

21 Comparability protocols offer the promise of a
22 standardized method for effecting certain application
23 changes without the need for prior agency approval, but the
24 scope of eligible changes and protocol contents remain
25 undefined. These tools and others, if used as intended, can

1 relieve the agency's application review burden for non-user
2 fee industries.

3 The blood action plan -- the blood action plan
4 holds promise for better communication of agency product
5 quality expectations to industry. Based on FDA's public
6 statements, the blood action plan calls for a rewrite of the
7 blood and plasma regulations. This includes formalizing
8 requirements published through guidance and memoranda into
9 regulations. CFRR applauds these efforts and hopes to work
10 with the agency in achieving these goals.

11 It is important to note, however, that no publicly
12 available documents currently exist to describe the blood
13 action plan. Time frames for achieving the plan objectives
14 have not been publicly announced, and industry input has not
15 been sought. One initiative of the plan is to develop a
16 pilot program for approval of certain blood and plasma
17 products through a monograph system. While this program
18 holds promise for both the FDA and industry in terms of the
19 application process, without an industry-FDA dialogue this
20 program may never get off the ground and an important
21 opportunity may be lost.

22 Product quality -- although GMPs are the
23 cornerstone of quality products, the blood and plasma
24 industries have lacked clear GMPs. Instead, the current
25 GMPs contain many references to biologics that often do not

1 directly bear on the blood and plasma industries. The
2 current GMPs applicable to blood and plasma products span
3 three sections of the Code of Federal Regulations, that is,
4 the 200 series, 600 series and 800 series. A comprehensive
5 rewrite of the GMPs is needed to incorporate these important
6 requirements into one set of unified regulations for blood
7 and plasma products.

8 Other regulatory requirements that bear on product
9 quality include error and accident reporting, adverse event
10 reporting, and product recalls and withdrawals. These tools
11 are under-utilized. Although industry expends vast
12 resources submitting error and accident reports, FDA has
13 failed to use this information as a quality assurance tool.
14 Quarterly reports of errors and accidents are published but
15 no meaningful analysis or trend reporting of submitted
16 errors and accidents has ever been made publicly available.
17 This is a missed opportunity. FDA can help industry better
18 itself by making this kind of information available.
19 Furthermore, error and accident reporting should not be
20 extended to other industry segments without careful
21 consideration.

22 Recalls and withdrawals are intended to help
23 ensure that only quality products reach patients. However,
24 the current recall regulations are not appropriate for blood
25 and plasma products. Many, if not most, blood and plasma

1 recalls involve only hypothetical risks, expired products or
2 already transfused products. Other tools such as recipient
3 notification may be more appropriate in such circumstances.
4 A more rational recall and withdrawal policy would save
5 agency resources and permit industry to concentrate its
6 resources on delivering high quality products.

7 In closing, I would like to say that CFRR
8 recognizes the magnitude of FDA's task -- ensuring that only
9 safe and effective products are made available to consumers.
10 Without adequate funding CBER cannot carry out this mandate.
11 Furthermore, this important mandate requires that the agency
12 retain individuals with extensive skills and technical
13 expertise. As such, CFRR fully supports CBER-based research
14 needed to maintain an appropriate scientific infrastructure.

15 Thank you for the opportunity to comment. CFRR
16 looks forward to working with the agency on current and
17 future regulatory initiatives. There is a copy of this
18 available as you exit. Thank you.

19 DR. ZOON: Thank you very much. This statement is
20 now open for questions or clarifications. Mary?

21 DR. GUSTAFSON: Roger, you mentioned that you
22 would like to see the GGP parameters broadened. Do you have
23 ideas on how that should be done? You indicated that you
24 encourage us to adhere to our good guidance practices and
25 you would also like to broaden the document's scope of

1 application.

2 MR. BRINSER: I don't have anything specific at
3 this point in time, but that is something we could include
4 in a further response.

5 DR. ZOON: Thank you very much. We very much
6 appreciate your comments. The next speaker is Emily
7 Rossiter, representing the Blood Technology Companies.

8 **Blood Technology Companies**

9 MS. ROSSITER: When I sent the agenda I put Blood
10 Technology Companies, not "the" Blood Technology Companies.
11 Let's treat this rather generically.

12 My name is Emily Rossiter, and I have been working
13 in the field of blood banking for over 25 years, first with
14 the American Red Cross and then as an independent consultant
15 for the last 15 years. I have never worked for FDA but I
16 have continuously been working with FDA on this side of the
17 table. Today, I appreciate the opportunity to act as
18 consultant to CBER on reform and reinvention.

19 [Slide]

20 I am joined in these comments today by the six
21 firms listed on this first slide, Haemonetics Corp., COBE
22 BCT, Inc., Terumo Medical Corp., Fall Corp., Genetic Testing
23 Institute, Inc., Gamma Biologicals, Inc., and six other
24 diagnostics, software and blood solutions manufacturers.
25 These companies all support these comments. These last six

1 firms specifically asked that their names be withheld.

2 [Laughter]

3 Some are clients, and I am sure that will trigger
4 a follow-up question. All support quicker patient access to
5 improved blood products and technologies through shorter
6 review times at FDA, and more constructive dialogue with
7 CBER policy staff. These companies make blood banking and
8 plasma related products, drugs, devices and in vitro
9 diagnostics that are reviewed by CBER and have been outside
10 user fee and fast track channels.

11 They are basically at the end of the line. They
12 do not make licensed biological products so their review
13 times are not covered in the licensed product review time
14 data that I think we have seen thus far. They have been
15 living in an environment in which their customers are under
16 extreme pressures to hoe the line on the cost of providing
17 blood for transfusion. I can speak personally for myself,
18 as well as them, when it comes to trying to work smarter in
19 an era of cost restrictions. We "feel your pain," FDA.

20 [Slide]

21 I would like to highlight four areas today
22 specifically for the CBER blood applications audience as you
23 brainstorm further ways to improve performance and meet
24 obligations under the new reform legislation. These areas
25 are review and response timetables, the extend and detail in

1 reports and submissions, the integration of related
2 submissions, and regulatory harmonization.

3 Most of the suggestions can be implemented at a
4 policy level without changes to regulation. They stem from
5 a philosophy that the quality of information coming in to
6 FDA is more important than the quantity; that time and
7 predictability, as I think Alan Goldhammer mentioned that
8 term, predictability, mean everything to companies in the
9 blood bank field as well; and that faced with limited
10 resources, further priority setting by CBER could redirect
11 staff time and efforts in constructive ways.

12 [Slide]

13 First and most importantly, review times for
14 blood-related drugs, devices and products need to be reduced
15 significantly across the board if we are to get them to the
16 patient. Six months should be the outside limit for any
17 review cycle, not just fast track products. Taking more
18 than six months in a field as dynamic as blood banking
19 creates a self-perpetuating problem -- the information is
20 out of date before it gets reviewed. This leads to
21 amendments, review letters and further response cycles and
22 further evolution of technology and FDA policy. The best
23 way out of this loop is to shorten turnaround so that
24 expectations and technology can be synchronized.

25 Review times for responses to warning letters or

1 other enforcement topics need goals too. If circumstances
2 warrant an FDA enforcement letter or action, calling for a
3 prompt response of, say, 10-30 days from industry, then
4 review by FDA within 2-3 months would be reasonable so that
5 customers and patients who could benefit are not left in
6 limbo.

7 [Slide]

8 Second, there are many areas of detail and
9 tradition that will come up for scrutiny during your
10 reinvention sessions, and I have listed some of my favorites
11 on this slide.

12 Let me first emphasize that I do not mean we
13 should reduce the level of detail available to FDA on site
14 or upon request. These suggestions affect the amount of
15 detail sent to FDA routinely for placing into a queue
16 somewhere review, response, and management. For example,
17 blood or plasma recalls -- all recalls are not equal. Many
18 blood or plasma recalls involving only hypothetical risks,
19 technical deviations or small numbers of expired products
20 could be relegated to market withdrawal status.

21 Error and accident reporting -- this program is
22 unique in its implementation in blood establishments, and is
23 over 20 years old I think. FDA has proposed extending error
24 and accident reporting to hospital-based transfusion
25 services, and recently highlighted its applicability to

1 licensed in vitro diagnostic manufacturers.

2 Before extending it, let's critically examine the
3 historical experience with the current program. Has it
4 served a critical need in the past years? We may find that
5 the more surveillance programs such as Medical Device
6 Reporting and the MedWatch Program, plus the existence of
7 industry-based quality programs for tracking and trending
8 may provide more modernized methods of getting useful
9 information.

10 "Me too" sites and products are another good area
11 to reduce paperwork without reducing safety for blood donors
12 or recipients. The addition of new apheresis collection
13 sites, or adding sites to make already approved blood
14 components in an organization that has already proved itself
15 should not be a major task for FDA review.

16 Similarly, the addition of modified blood products
17 such as irradiated or leukocyte-reduced products should not
18 be a major exercise, and by major exercise I mean prior
19 approval supplements for each location, pre-approval
20 inspections, and the like.

21 CBER staff have embraced the concept of report
22 simplification and reduction, trying to ease the process by
23 which changes can be made to existing products. But more is
24 needed. More downgrading of changes to 30-day notice and
25 annual report is both possible and necessary to allow CBER

1 staff to focus on larger, more critical issues.

2 [Slide]

3 Third, the integration of approval processes for
4 new blood product license supplements with drug and device
5 clearances would speed technology to improve patients. The
6 slide behind me explains, hopefully -- or helps to explain
7 what I mean by this.

8 The top three boxes on this slide represent
9 technologies used to collect or process blood or plasma from
10 donors. Several companies make blood processing solutions
11 and disposable, single-use plastic bag sets which are used
12 along with filters and separators and expressers, which I am
13 generically calling instruments, to make blood products for
14 transfusion, depicted on the bottom three boxes.

15 Typically, the storage solution, in the upper left
16 of the slide, undergoes a drug approval process in the U.S.,
17 that is, a new drug application or abbreviated new drug
18 application, and the processing containers along with any
19 related instruments undergo device clearance, either a
20 510(k) or premarket approval. A pre-approval inspection may
21 also be required.

22 Obtaining premarket clearance for these
23 technologies in the top three boxes in recent times has
24 taken anywhere from two to over ten years whether they are
25 new generations of technologies, "me too" or modest

1 improvements. If these solutions and devices are destined
2 for use directly in patient care or in unlicensed blood
3 banks, these clearances are the only ones needed from FDA,
4 but if the same solutions or sets are to be used in a
5 licensed blood center, and the blood products are shipped in
6 interstate commerce, we are only half way there. Another
7 premarket approval and pre-license inspection cycle is often
8 required, sometimes for each of the products on the lower
9 slide and for each location or facility. This adds another
10 few years of delay to the availability of the resulting
11 blood product interstate. This means that patients served
12 by unlicensed intrastate blood banks can benefit from newer
13 technologies several years before patients served by
14 licensed facilities, which is the majority of patients.

15 Over the years, FDA has used guidance documents
16 and notifications to facilitate licensed blood center use of
17 new technologies. For example, in infectious disease marker
18 testing. There is room to expand this practice where
19 technology has a proven track record for many years, or where
20 the benefits clearly outweigh the risks.

21 [Slide]

22 Finally, further harmonization will help blood
23 technology improvements reach the patient. Areas where
24 CBER, CDRH or CDER regulates similar technologies for
25 similar uses should be analyzed, and the lowest common

1 denominators found for a more unified approach to regulatory
2 policy and enforcement. These areas include parenteral
3 solutions, instruments in vitro diagnostics, single-use
4 disposable products, and computer software programs.
5 Differences among the regulatory policies for these projects
6 should be held to scrutiny, perhaps by external advisory
7 groups, and the differences eliminated unless they can
8 adequately be defended by science, not emotion.

9 FDA's ongoing efforts at international
10 harmonization are encouraging. In the area of blood
11 banking, an analysis of the risks and benefits of the
12 European Community's policy toward blood processing
13 solutions as device accessories, versus FDA's drug approach,
14 might reveal some useful information during the reinvention
15 deliberations.

16 Ultimately, international harmonization efforts
17 should continue until a single global dossier is recognized
18 for all blood and plasma products, related drugs and
19 devices.

20 [Slide]

21 Before closing, I want to recognize some of the
22 recent successes of FDA and CBER. First, the FDA Home Page
23 and Internet sites have greatly improved industry's ability
24 to stay up to date and monitor developments in a timely
25 fashion. Continuing efforts to enhance the information,

1 adding search capability and better links and organizations
2 should continue.

3 Second, to CBER blood staff, the open door and
4 open telephone policies that you have consistently tried to
5 maintain are absolutely essential to progress and a safe
6 blood supply. It has been difficult to accommodate the
7 mounting requests that have resulted from your current
8 workload, but it is important that you know that each
9 personal contact with industry is regarded as a precious
10 investment in the future.

11 Thank you.

12 DR. ZOON: Thank you very much. Are there any
13 questions or clarifications? No? Thank you very much. Our
14 last speaker in this panel is Sharon Leiser, QA, Regulatory
15 Affairs, American Red Cross.

16 **American Red Cross**

17 MS. LEISER: Good morning Dr. Zoon, Ms. Suydam,
18 FDA staff, and fellow members of the regulated community.
19 My name is Sharon Leiser, and I am here speaking on behalf
20 of the American Red Cross which supplies approximately one-
21 half of the nation's supply of transfusable blood
22 components, approximately 20 percent of the nation's plasma
23 derivatives, approximately 20 percent of the nation's tissue
24 for transplantation purposes, and which is supporting the
25 agency's current effort for the provision of stem and cord

1 cells. Thank you for providing us with the opportunity to
2 speak today.

3 As a member of the Coalition for Regulatory
4 Reform, the American Red Cross fully supports and agrees
5 with the points made today by Mr. Brinser, the
6 representative for the CFRR. American Red Cross also wants
7 to emphasize several points about the implementation of the
8 FDA Modernization Act that I will be touching on today. The
9 American Red Cross will also provide written comments which
10 will expand on some of these points.

11 We wish to commend you, FDA, on your efforts to
12 date. First, we have seen, for example, a substantial
13 improvement in the blood licensure submission review
14 process. The review of ARC submissions has been reduced
15 from a backlog of over 900 open cases in 1995 to a current
16 open caseload of only a few dozen. In addition, the review
17 period for submissions has decreased approximately 50
18 percent in only a two-year time period. These improvements
19 benefit the public by increasing our ability to manufacture
20 better and more efficacious blood components and plasma
21 derivatives and supply them to those in need.

22 Second, we are encouraged by the information
23 recently presented on the blood action plan. We see this
24 plan as the start of a potentially beneficial program for
25 the agency, for the regulated community, and for the public

1 which relies on us and on the FDA to provide the safest
2 blood in the world. We are particularly excited by the
3 agency's initiatives to update the regulations and guidances
4 for blood and blood products. We eagerly await publication
5 of the blood action plan and our opportunities for further
6 participation in the plan's development.

7 The American Red Cross strongly endorses efforts
8 towards open communication between the FDA, consumer groups,
9 industry, and professional societies such as AABB. There
10 has been considerable headway in this arena, particularly
11 with the increased use of the Web and other electronic
12 communication mechanisms. We also encourage the FDA to
13 expand an effective communication policy to all levels of
14 FDA and CBER by reexamining the current practices for
15 working with the regulated community and other groups.

16 For example, both the regulated community and the
17 FDA need to work in a more open style of addressing issues
18 by directing our approaches toward resolution as partners.
19 We encourage continued interaction between the FDA and work
20 groups such as the CFRR to seek resolution of outstanding
21 issues such as those relating to adverse reactions, errors
22 and accidents and product retrievals. We also suggest
23 reevaluation of the requirements for participation, as
24 appropriate, by national FDA staff in professional meetings
25 that are sponsored by the regulated community or other non-

1 government entities to allow for more participation.

2 I would like to turn now to some of FDA's specific
3 questions listed in "A Message to FDA Stakeholders." The
4 agency asked what could be done to improve the submission
5 review processes, to sustain an effective, timely, and
6 science-based postmarketing surveillance system, to
7 adequately meet increasing demands, and to eliminate
8 backlogs in the review process. As noted earlier, we have
9 already seen vast improvements in these processes.

10 One of the innovations about which we are most
11 encouraged is CBER's implementation of the new comparability
12 protocol process which will be used in conjunction with the
13 revised system of ranking and grading licensure submissions.
14 This system is the first step in creating a review process
15 which will meet the needs of both the biologics industry and
16 the public's health and safety in the 21st century.

17 We encourage the rapid development and completion
18 of this and other initiatives. In particular, we would
19 like to see clear guidelines for the use of the
20 comparability protocol process. We also encourage the FDA
21 to think even more innovatively in addressing the following:

22 providing clear guidance about the requirements
23 for the new annual report process;

24 improving the ranking and grading of specific
25 blood and blood products as the foundation of the blood

1 licensure review process;

2 without compromising the public input process,
3 creating a system for making quick changes to guidances as
4 scientific and technical knowledge expands;

5 expanding the regulations to directly reference
6 blood and blood products instead of trying to fit them into
7 a system with which they do not harmonize; and,

8 creating an innovative staff incentive/reward
9 system that will foster new ideas and speedier reviews
10 without compromising quality and effectiveness.

11 I want to specifically talk about improving the
12 ranking and grading of products. First, the agency should
13 define what information is necessary to evaluate the
14 licensure submission reviews. Second, the submissions and
15 reviews should be tiered based on hazard and impact. We
16 believe that, in following this approach, the demands on the
17 agency will be reduced thereby increasing FDA's ability to
18 focus resources on new products. For example, there are
19 many blood products, like red blood cells, platelets,
20 platelet pheresis, which have been in the public arena for a
21 long time. Their qualities, including efficacy and
22 manufacturing specifications, are well known. It is
23 reasonable that licensure submission requirements for these
24 well-known products could be placed on the lowest review
25 tier, and compliance confirmation could be based on post-

1 licensure sampling audits instead of licensure. The
2 greatest amount of resources could then be transferred to
3 completely new products like red blood cells pheresis.
4 Then, as these new products become mainstream, their ranking
5 and tier of review could be lowered to allow for other new
6 products to absorb review resources.

7 On the FDA question about what approach the agency
8 should use to assure an appropriate scientific
9 infrastructure, we want to emphasize that we, as well as the
10 rest of the regulated community, wish to work with FDA
11 regarding creative and innovative ways to use scientific
12 expertise. We recommend that there be staff exchange
13 programs with academia, other government agencies such as
14 NIH, CDC, and the National Science Foundation, and industry
15 research organizations, to share staff, expertise, and
16 research results. The idea is that by fostering better
17 understanding of applicable science in a cross-cultural
18 setting, we can simultaneously assure an appropriate
19 scientific infrastructure which utilizes the most current
20 knowledge and also promotes staff development.

21 I would like to briefly touch upon a point I
22 mentioned earlier concerning approaches to improving error
23 and accident reporting. This is an example of a regulatory
24 program which might benefit from expanded public input
25 beyond the regulated community. American Red Cross, in

1 developing its own program, consulted with Hal Kaplan from
2 the University of Texas, Southwestern Medical Center at
3 Dallas. Dr. Kaplan has suggested a system modeled after a
4 classification for causal factors with multiple applications
5 including transportation, nuclear power, and the
6 petrochemical industry. Information would be submitted to
7 an independent agency and shared among the regulated
8 community for the mutual benefit of its members and the FDA.
9 We also encourage, as part of its implementation of the
10 Modernization Act, that you search out ideas and innovations
11 from other fields which might be applicable to the FDA
12 system.

13 We believe the FDA's initial efforts in meeting
14 the requirements and demands contained within the FDA
15 Modernization Act merit considerable recognition and praise.
16 Thank you again for this opportunity to participate, and we
17 look forward to future efforts to partner and build a new
18 system together.

19 DR. ZOON: Thank you very, very much. Are there
20 any questions or clarifications? Becky?

21 MS. DEVINE: You had mentioned adding blood to
22 some specific regulations, that they didn't fit in certain
23 places. Could you expand on what areas you were thinking
24 about in that regard?

25 MS. LEISER: One big area is recalls. An example

1 is stock recovery. The definition says that you can only
2 perform one if none of a lot has been released. Well, a lot
3 is an entire blood unit and we have different expiration
4 dates for different components. So, under that definition
5 we can never perform a stock recovery.

6 Otherwise, we will further expand upon this in our
7 response to the docket. Roger also mentioned, when he
8 talked about three sections that are used for blood and,
9 yet, really do not apply to blood.

10 DR. ZOON: This will be very helpful. We look
11 forward to your additional comments to the docket. Mark?

12 MR. ELEGOLD: I have one question. In the next
13 to the last paragraph, in the discussion of an alternative
14 system where reports would go to an independent agency, an
15 independent group for classification as to causal subjects,
16 would that replace the error and accident reporting to FDA
17 or be in addition to it?

18 MS. LEISER: We are looking at it as a
19 replacement.

20 MR. ELEGOLD: Well, in the cases where an error
21 or accident led to a violative product, we use those for
22 leads to potential recalls or other actions. What would the
23 link be to us for following up on violative product in the
24 marketplace?

25 MS. LEISER: I think it would be the same link as

1 now. This would be like contracting out a service. It
2 would not be an agency that is blind to FDA. FDA would have
3 access to any information as with any other regulated
4 biologics manufacturer. For more information though, we
5 will submit more to the docket. I am not totally cognizant
6 of this area.

7 MR. ELENGOLD: I was just curious because it would
8 look like that if it went to a third party that would lead
9 to a delay of triage and reporting to another triage and
10 reporting system within the agency. Very often these
11 reports do lead to our ability to monitor withdrawal of
12 violative products. So, I would be interested in seeing
13 that submitted as well. Thank you.

14 DR. ZOON: Thank you. Mr. Chesebrough?

15 MR. CHESEBROUGH: I was wondering if you could
16 expand on your comment, on page three, with respect to
17 reevaluation of the requirements for participation by
18 national FDA staff in professional meetings sponsored by the
19 community to allow for more participation. What do you see
20 as some areas there, and what are you hoping for?

21 MS. LEISER: Well, there may be budgetary
22 barriers, but we find that national staff is not always
23 permitted to travel long distances to participate in
24 meetings. When we say participate we mean presentations.
25 There was a large meeting, sponsored by various sectors of

1 the regulated community, last January in New Orleans. We
2 did have FDA participation but there was a lot of red tape
3 that had to be gone through to get that participation. So,
4 we feel that we can't learn from you if we can't get you.

5 DR. ZOON: There is a question in the back.
6 Please identify yourself.

7 MR. BINION: Steve Binion, with the Femwal
8 Division, Baxter Healthcare Corp. Actually, I just have two
9 quick comments and a clarification, referring back to
10 Emily's presentation.

11 On behalf of Femwal, I would like to commend CBER
12 on the extensive use of Internet communication tools. I
13 would also indicate that we too generally favor moves toward
14 global regulation of blood and blood technology products.
15 We will be making separate comments to the docket.

16 Then, just in case there was any suspense element
17 involved, Baxter was not one of the six --

18 [Laughter]

19 Thank you.

20 DR. ZOON: Thank you very much. Are there any
21 other comments? If not, I wish to thank you very, very
22 much. I appreciate those very thoughtful comments. I am
23 actually going to proceed with the next panel. So, I would
24 like to thank our current panelists very much and invite the
25 next set of panelists to the table.

1 I would also like to take this opportunity to
2 introduce Jay Seigal. He is the Director of the Office of
3 Therapeutics Research and Review.

4 Are you ready to begin or do you need a little
5 more time? No? Well, we have our next panel that
6 represents a number of biotech companies, and I would like
7 to first introduce Janice Bourque, Executive Director of
8 Massachusetts Biotechnology Council.

9 **Massachusetts Biotechnology Council**

10 MS. BOURQUE: Thank you. Thank you for letting us
11 attend and have this public session so we could speak.

12 [Slide]

13 As she mentioned, I represent the Massachusetts
14 Biotechnology Council, and I have with me today Jim Easton,
15 who is Vice President of Government Affairs and Strategic
16 Policy from one of our member companies, BIOPURE, as well as
17 Sheila Flaherty, who is Associate General Counsel of the
18 Legal Department of Astra USA. We speak collectively on
19 behalf of our members, and the comments we have were drawn
20 not specifically from any individual company per safety and
21 efficacy but as a collective response.

22 [Slide]

23 For those of you who don't know, the Massachusetts
24 Biotechnology Council has been around for about 13 years,
25 and we have worked very hard in trying to ensure that the

1 biotech companies in Massachusetts have a way to reach their
2 full potential, and often we represent them in a number of
3 different ways and this is one of them.

4 We have approximately over 200 companies, and most
5 of them are small to mid size. We have several large ones
6 that most of you are aware of, and most of them have
7 products that run from early stage development to
8 commercialized products.

9 [Slide]

10 The MBS supports the FDA in its FDAMA mission to
11 realize the prompt approval of safe and effective new drugs
12 and other therapies. Obviously, the main goal for both of
13 us is to get these products as quickly as possible to
14 patients because that is really what our aim is, to try and
15 alleviate any type of suffering that they might have.

16 [Slide]

17 I won't spend any time on the FDAMA objectives.
18 That was already done earlier this morning by Linda. But
19 these are the six that she covered well.

20 [Slide]

21 So you can understand the process of what we did
22 with these 200 member companies, we have excellent resources
23 in terms of regulatory experts who live and breathe this
24 type of work every day, and they came together and tried to
25 identify collective concerns, common concerns that they

1 thought we could bring with us today, and to propose some
2 recommendations.

3 [Slide]

4 Specifically, there were five areas that we wanted
5 to address: the performance goals, user fees and meetings,
6 manufacturing changes, fast track issues, off-label uses and
7 pharmacoeconomics. On a more global, over-arching
8 mechanism, we wanted to address the issue of harmonization
9 consistency within the agency, increased transparency, and
10 the enhancement of the role of the ombudsman in cooperation
11 with the FDA and the industry.

12 [Slide]

13 The result of which was a White Paper that we
14 developed and submitted to the FDA, and there are specific
15 areas that were identified by the FDA of individuals who
16 were responsible for helping implement the five areas that
17 we are addressing and this document was submitted to them as
18 well. It was broken into points to consider documents, as
19 well as recommendations on our common concerns.

20 [Slide]

21 Today, what we would like to do is to address
22 these specific five areas, and Jim, myself and Sheila will
23 do that in sort of a panel format. We won't individually
24 stand up here and speak; we are going to speak from a panel
25 over here.

1 The first two sections, 119 and 116 for meetings,
2 performance goals and manufacturing changes, will be
3 addressed by Jim Weston. I will then address fast track and
4 Sheila will address off-label use and healthcare economic
5 information. Then, I will close with some of the over-
6 arching concerns that we have and recommendations. So, I
7 will turn it over now to Jim.

8 [Slide]

9 MR. WESTON: As Janice mentioned, each of these
10 working groups picked a specific section of FDAMA to
11 address, and in addressing each of these sections we took a
12 look at specifically what we were trying to accomplish by
13 addressing the section. Starting with the meetings and
14 performance goals, Section 119, we had a key objective of
15 being able to look overall at how we could improve the
16 process which would provide delivery of breakthrough
17 products to patients in a time-sensitive manner.

18 Specifically, we are addressing how we could
19 establish agreements on the design of clinical trials and
20 preclinical studies in meetings; how to resolve any issues
21 that occurred in a timely manner; and also how to maintain
22 consistency in the review process. These were specific
23 agreements which we provided in our document to be able to
24 do that with the resource limitations of the agency.

25 [Slide]

1 In coming out of that then, we had some specific
2 guidance documents in our points to consider. Specifically,
3 we talked about the ability to have obligations of both the
4 sponsor and the FDA regarding setting up meetings. For
5 example, in setting up meetings we used the classification
6 of the A, B and C meeting types of setting defined time-
7 lines of either 30, 60 or 75 days to have a meeting after it
8 has been requested. Specifically, though, in the whole
9 concept of fast track, which we will talk about later, a
10 fast track product, we requested that those in all cases
11 have a 30-day limitation because of the priority of doing
12 it.

13 In terms of holding meetings, one of the key
14 provisions is the ability to have common minutes from
15 meetings. FDA has been requested to provide minutes of
16 meetings within 30 days, but also then the sponsor will be
17 given 10 days to be able to review and comment on those
18 meetings as necessary.

19 In terms of the types of meetings, we agreed that
20 there ought to be a classification for different types and,
21 specifically for fast track, those meetings should always go
22 to the higher standard in all cases.

23 For performance goals also we looked at the
24 ability to have feedback from the specific meeting type of
25 information, and specifically having monthly updates on a

1 progress report of a submission, specifically a fast track
2 submission.

3 [Slide]

4 We also looked at the section dealing with
5 manufacturing changes. This is Section 116. Here, our goal
6 was to be able to clarify certainly the major and minor
7 changes, and be able to have uniformity of change
8 classification throughout many of the documents, and to be
9 able to provide a guidance document, not necessarily a
10 regulation but a guidance document.

11 Historically, there have been many types of
12 approaches to this in existing guidance documents. The
13 three-tier approach appears to be the most common one going
14 forward.

15 [Slide]

16 We basically embodied that by going forward with
17 the three-tier approach, and compliment CBER on their
18 ability to have this in many of their existing documents.
19 But dealing basically with changes, a substantial change
20 will require pre-approval for it; a moderate change to a
21 product, which is a supplement with a notice, typically a
22 30-day review period; and a minimal change, which is
23 obviously notice in an annual report.

24 The concept of a comparability protocol is also a
25 very important concept which we embody and need to have

1 defined. We proposed specific guidance in our document
2 dealing with tests and acceptance criteria in the process
3 for a comparability protocol.

4 Obviously, in terms of changes, we are embodying
5 many of the existing CBER regulations dealing with label
6 changes.

7 [Slide]

8 MS. BOURQUE: With regards to the fast track
9 section, we would like to suggest that the PDUFA-II
10 performance goals that have been stated would be first
11 applied to fast track, the point being that if you have a 60
12 percent performance goal requirement, perhaps 90 percent of
13 that 60 percent could be comprised of fast track approvals
14 and review, the point being that obviously when you address
15 fast track we are talking about serious and life-threatening
16 issues or unmet medical needs.

17 [Slide]

18 Obviously, give the resources that you might have,
19 we would always challenge and encourage FDA to exceed that
20 goal when it came to fast track items.

21 [Slide]

22 In terms of definitions, there are two types of
23 definitions that would need further clarification and
24 development, one being serious and life-threatening
25 conditions. In the 1992 Federal Register notice, and again

1 reiterated in FDAMA, there was a broad and flexible
2 interpretation of just what that would be. We would like to
3 recommend that those broad and flexible interpretations be
4 adopted throughout the agency, with a consistent use in all
5 the divisions, primarily because there have been comments
6 that have been made that perhaps only AIDS and cancer are
7 considered serious and life-threatening and we would like to
8 suggest that perhaps there are other diseases that might fit
9 that as well.

10 Secondly, with regards to the definition of the
11 potential to address unmet medical needs, obviously if there
12 is no treatment there is an unmet medical need. We would
13 like to suggest and recommend that perhaps there is an unmet
14 medical need for diseases that already may have an imperfect
15 though existing treatment. I would like to give you a
16 couple of examples.

17 Let's suppose that an existing treatment can offer
18 a patient temporary clinical benefit but the new treatment
19 might be able to provide a longer term clinical benefit.
20 Or, suppose that perhaps the existing treatment only
21 alleviates the symptoms of a disease but that the new
22 treatment would, in fact, be able to address the underlying
23 pathology of that disease. Perhaps there are great side
24 effects and risks associated with an existing treatment and
25 the new product would be able to provide a safer or more

1 tolerable treatment for the patient.

2 Another example might be perhaps an existing
3 treatment comes from products that are human or animal based
4 and perhaps a recombinant product might provide a safer
5 mechanism of product where you don't have the possible
6 transmission of virus issues.

7 This, obviously, is not a complete list but it is
8 suggestions and ideas that we have on how you might be able
9 to define unmet medical needs.

10 [Slide]

11 With regards to endpoints, specifically surrogate
12 endpoints, obviously there are two types of endpoints that a
13 sponsor can utilize in trying to demonstrate an effect. One
14 would be on an unvalidated surrogate endpoint, and the
15 second would be on a clinical or validated endpoint.

16 With regards to fast track, we would like to
17 suggest that perhaps if a sponsor is utilizing an
18 unvalidated surrogate endpoint that, in fact, is reasonably
19 likely to predict clinical benefit, this particular type of
20 program would be subject to the post-approval requirements,
21 and that those post-approval requirements actually would be
22 those of subsection (b) (2), and these subsection
23 requirements would apply to fast track and not create a new
24 grouping of post-approval requirements.

25 Secondly, if the sponsor is using a clinical or

1 validated clinical endpoint, in fact, they should be able to
2 receive regular approval and not be subject to the post-
3 approval requirements of subsection (b)(2). So, essentially
4 what we are recommending -- and I believe, PhRMA at an
5 earlier point had suggested sort of a two-track system
6 whereby the sponsors who are using clinical endpoints can
7 obtain fast track benefits without sacrificing the benefits
8 of a regular approval.

9 We also recommend that the guidance documents
10 should include discussion about the various items I will
11 speak about. The selection and recommendations to the
12 sponsor and the selection process of surrogate endpoints --
13 perhaps what could happen, there could be quarterly
14 conferences in which the industry could actually propose
15 what these surrogate endpoints could be and introduce them
16 and discuss them with the FDA.

17 More specifically, we would like to recommend that
18 there are two specific areas that might require some
19 attention. One would be those for chronic or degenerative
20 type diseases which, obviously, require longer or larger
21 clinical trials. The second would be for those surrogate
22 endpoints that have broader applicability to a class of
23 technologies such as with gene or cell therapies.

24 This guidance document that is going to be
25 developed also should give recommendations and guidance to

1 the sponsor and the use of professional societies and
2 academic resources with regards to quality of life scales as
3 perhaps the primary clinical endpoint and with regards to
4 dissemination of information of surrogate endpoints.

5 In terms of the designation of a product for fast
6 track, we would recommend that this designation would be by
7 the directors of the review divisions. We feel that they
8 have the most hands on and direct knowledge, and would be
9 able to make very good decisions with regards to which
10 products should be tracked in a fast track program.

11 We would also suggest that withdrawal of this
12 designation would be based on two circumstances. One
13 circumstance would be whereby the sponsor would demonstrate,
14 via a pivotal clinical trial design, that it is no longer
15 pursuing an indication for a serious or life-threatening
16 disease. The second circumstance for withdrawal would be
17 after an advisory panel meeting and a complete review of the
18 NDA or BLA that the FDA determines that a product does not
19 meet an unmet medical need.

20 We would recommend that prior to any type of
21 withdrawal of the fast track designation that they give the
22 opportunity to first notify the sponsor of that desire, and
23 that the sponsor have an opportunity to meet informally with
24 the FDA prior to that final notification.

25 Obviously, as was brought up earlier with regards

1 to the IND with the fast track, you have the opportunity to
2 request fast track designation whether you are filing your
3 IND or throughout the process or at your NDA or BLA status.
4 We would recommend that with regards to the IND process that
5 once fast track status is designated that the sponsor and
6 the FDA meet within the first 60 days to really begin the
7 dialogue and the process of understanding what all the
8 requirements would be.

9 We would suggest that they develop a general
10 schedule with major action dates and milestones so that both
11 parties are very clear on what is expected. We have also
12 offered time-lines in terms of should either party not be
13 able to respond within that general schedule.

14 Additionally, we are asking that the sponsors try
15 to seek early approval on the protocol and agreement on the
16 protocol. Often some of our companies have experienced
17 situations whereby a protocol was agreed upon. There was a
18 change in reviewers, for whatever reason, and then suddenly
19 the company is faced with that protocol no longer being
20 acceptable. So, we would like to get that up front and
21 early.

22 With regards to fast track and the NDA and BLA
23 submissions, the nice mechanism triggers this rolling review
24 opportunity. What that means is that companies have the
25 ability, obviously, to submit portions of their application

1 to the FDA so that they can get decisions made on those
2 facets of them. We feel that is a great way to maximize the
3 utilization up front and minimize the time at the final end
4 when you come to final approval.

5 We would also recommend, however, that there be
6 some kind of information system or tracking system so that
7 the companies are able to track the status of their NDA and
8 BLA through the process and would know at any point in time
9 where exactly they are.

10 [Slide]

11 With regards to alternative standards for
12 marketing, this really pertains to subsection (b) (2) where
13 the products are approved on the basis of their clinical or
14 surrogate endpoint that is reasonably likely to predict
15 clinical benefit. We believe it was the congressional
16 intent that this would apply to unvalidated data regardless
17 of whether it was a surrogate or clinical endpoint.

18 Let me give you an example. Let's suppose a
19 product was able to demonstrate it had a 93 percent
20 confidence interval. The current standards require a 95
21 percent confidence interval. Well, 93 percent, we believe,
22 would qualify for reasonably likely to predict clinical
23 benefit.

24 The subsection (b) approval would require,
25 obviously, a post-approval study to validate that efficacy

1 and we feel that would be appropriate.

2 I guess our point here -- and this was well stated
3 in the earlier FDA subpart (e) regulation whereby perhaps a
4 90 percent chance of effectiveness is always better than
5 none at all. So, the issue comes to whether the standard of
6 95 percent in terms of safety and efficacy in trying to
7 determine reasonably likely to predict clinical benefit,
8 that there might be other things that may be taken into
9 consideration there when it doesn't meet the 95 percent
10 standard.

11 With regards to post-approval requirements, again,
12 this has to do with subsection (e). The FDA may, but it is
13 not mandated to require Phase IV studies or for the pre-
14 approval of the marketing literature -- we feel that with
15 the pre-approval of the marketing literature, the pre-
16 approval process should be terminated six months after the
17 product has been approved unless, of course, the sponsor is
18 demonstrating somehow a pattern of inappropriate promotional
19 activity.

20 [Slide]

21 MS. FLAHERTY: I would like to talk to you very
22 briefly today about two further sections of FDAMA, and give
23 some of the Mass. Biotech. Council's recommendations to the
24 FDA for implementation of those two areas.

25 Both sections deal with the dissemination of

1 information by industry to healthcare providers and to
2 formulary committees. The first area is Section 401 which
3 deals with off-label use.

4 The key objective, as we understand the statute,
5 of Section 401 is to provide healthcare professionals with
6 the best information available to treat patients and to make
7 informed healthcare decisions.

8 [Slide]

9 We submitted comments to the FDA on their proposed
10 regs. that they have already promulgated to implement this
11 section, and our comments on those regs. were submitted on
12 July 23, 1998. Today, I will give you just a few brief
13 highlights.

14 MBC feels that the criteria for acceptable journal
15 article and reference texts under the proposed regs. is too
16 restrictive in comparison to the criteria outlined in the
17 statute itself. The statute requires that the article to be
18 disseminated should be about a clinical investigation that
19 would be considered scientifically sound by experts.

20 MBC does not have any problems with this
21 recommendation or requirement under the statute, however,
22 the proposed rule requires an additional level of detail
23 beyond that which is usually included in published reports.
24 So, we are afraid that certain articles that are, indeed,
25 about clinical investigations that aren't considered

1 scientifically sound by the experts would not be eligible
2 for distribution under this proposed rule.

3 The second portion of the proposed rule that we
4 would like to comment on is the requirements for mandatory
5 disclosures. The proposed rule sets forth a specific
6 mandatory disclosure requirement that must be included on
7 every journal article, regardless of the content of that
8 journal article. While the statute itself does require
9 disclosures, and the MBC is not opposed to including
10 disclosures, we feel that industry should have a little bit
11 of discretion to tailor those disclosures to appropriately
12 give the healthcare professional the information about what
13 the specific limitations are, or the specific problems, or
14 information in the article that is dealing with off-label
15 uses.

16 The second disclosure provision of the proposed
17 regulation requires that with any additional information the
18 FDA requires the manufacturer to include that information,
19 including bibliographic statements, other articles or
20 specific statements by the FDA to be attached on the front
21 of the article. We think those specific attachment
22 requirements are too restrictive in the sense that they
23 could potentially mean that the information that the
24 manufacturer is trying to get out to physicians is at the
25 bottom of a pile that the physician will never get to.

1 What we would propose is that if we are required
2 to submit this information along with the article we are
3 wanting to distribute, we are happy to do that but we think
4 the FDA should leave it to the industry to just ensure that
5 we include that information and not have specific
6 requirements as to where and how that information should be
7 attached or presented.

8 A third issue with the proposed rule is the
9 definition of economically prohibitive. The statute
10 provides for an exception in instances where it would be
11 economically prohibitive for a manufacturer to actually
12 submit an SNDA for the proposed off-label use.

13 While we acknowledge that that limitation or
14 exception in the statute is, indeed, a very limited
15 exception, the proposed reg. itself effectively eliminates
16 any such exception. In other words, if a manufacturer is
17 not going to submit an SNDA they would not be able to
18 disseminate information under Section 401.

19 The next point that we have is the narrow
20 definition of unapproved uses. We are concerned that the
21 definition of unapproved uses in the regulation tends to say
22 that you can only talk about uses that are explicitly in
23 your labeling, otherwise it is an unapproved use. In many
24 instances specified dosages for other information is
25 included in pivotal studies and is submitted to the FDA but,

1 as we are negotiating the labeling of that particular
2 product, we may or may not include everything in those
3 pivotal studies. We would suggest that the unapproved use
4 definition be expanded to include information from our
5 pivotal studies that were the basis for our approval in the
6 first place.

7 Finally, we would ask that the FDA consider
8 permitting Internet reporting for some of the reporting
9 requirements under the statute. The industry will be
10 required to keep a list of who they disseminated the
11 information to and what specific information was
12 disseminated. We would request that the FDA permit us to
13 either submit that electronically to them over the Internet
14 or, alternatively, that we be permitted to post that
15 information on our Internet site.

16 We would also like to suggest to the FDA one means
17 of getting around the potentially burdensome problem of
18 distributing numerous disclaimers, other articles or FDA
19 statements. We would be willing, or we would suggest that
20 you permit industry, on the reprint, to include our Web site
21 address and indicate that there is, you know, further
22 information included on our Web site, in much the same way
23 as direct consumer advertising permits the use of the Web
24 site address to direct the consumer to additional
25 information.

1 Finally, PhRMA submitted separate comments on this
2 regulation to the industry which we, in the MBC and our
3 working groups, reviewed carefully. We would just like to
4 urge the FDA to adopt as many of PhRMA's proposals as they
5 find acceptable because we endorse them wholeheartedly.

6 [Slide]

7 The second section dealing with dissemination of
8 information in FDAMA that we would like to talk to you about
9 today is Section 114, which deals with the dissemination of
10 healthcare economic information.

11 The key objective of the statute, as MBC sees it,
12 is that the congressional intent was to provide economic
13 data to support managed care organizations, integrated
14 delivery systems, and other organizations in their drug
15 selection decisions. Basically, these managed care
16 organizations and other delivery systems and hospital buying
17 groups ask industry for this information on economic data
18 all the time. They are making their decisions based on
19 economic information anyway, whether we give it to them or
20 not, and sometimes that economic information is anecdotal
21 rather than scientific based. That is why Congress included
22 this provision.

23 [Slide]

24 The FDA is in the process, I believe, right now of
25 drafting a guidance to implement this provision, and MBC

1 would urge that that guidance follows the intent of the
2 statute and I will just highlight a few of the points.

3 The statute now changes the standard for
4 substantiating healthcare economic information to a
5 competent and reliable scientific evidence standard. What
6 that means is basically that no longer do you need to submit
7 two adequate and well-controlled studies to support your
8 healthcare economic data. If you have competent and
9 reliable scientific evidence, which could be one well-
10 controlled study or another adequate other type of study
11 instead of a head-to-head clinical study, you should be able
12 to support your healthcare economic claims.

13 There are certain limitations on Section 114 that
14 permit the use of this lowered standard. Those limitations
15 are that you are only allowed to talk about healthcare
16 economic information that is directly related to an approved
17 indication -- in other words, no off-label discussions, or
18 you can't use healthcare economic information, or you can't
19 provide it on off-label uses.

20 The second is the permitted audience, a very
21 restricted audience that would be eligible to receive this
22 information from the manufacturer. There would be formulary
23 committees or other managed care organizations or healthcare
24 buying groups who would be making those decisions. In other
25 words, you couldn't provide that information to single

1 physicians who are prescribing directly to patients or to
2 consumers of the products themselves.

3 We would also urge the FDA to adopt a definition
4 of healthcare economic information that includes all forms
5 of that information where that information is intended to
6 facilitate decision-making at the formulary level. That
7 would include cost analysis, cost effective analysis, and
8 cost benefit analyses.

9 We would urge the FDA to permit manufacturers to
10 use reasonable assumptions with the healthcare economic
11 consequences derived from the approved indication, rather
12 than just clinical endpoints.

13 [Slide]

14 We would also urge that healthcare economic
15 information could be supported by clinical outcomes that
16 would include many different areas, such as the physiologic,
17 anatomic, biologic endpoints as well as health status,
18 quality of life measures, life expectancy, patient
19 performance, patient satisfaction, compliance, and other
20 such measures that are relevant to these formulary committee
21 members and others when they are making decisions of what
22 drugs to put on their formularies.

23 I would also recommend that the FDA permit us to
24 disseminate information in many different ways, using both
25 printed material, computer-based material, interactive

1 software, etc.

2 Finally, MBC would urge the FDA to use experts to
3 evaluate the substantiation, the information, whether it is
4 modeling, meta-analysis. Healthcare economics is a vital
5 new area of study and we would urge the FDA to use experts
6 in the field when they are evaluating healthcare economic
7 claims.

8 Finally, I would just like to also say in this
9 regard that PhRMA has submitted a guidance for industry to
10 the FDA for their consideration in drafting the guidance
11 and, again, we support and urge you to endorse PhRMA's
12 recommendations.

13 [Slide]

14 MS. BOURQUE: In closing, there were three over-
15 arching general concerns that the industry had with regards
16 to recommendations to the FDA, and those three I mentioned
17 earlier were the harmonization and consistency of the
18 handling of drugs and biologics; the second, the increased
19 transparency and accountability within FDA, and the
20 cooperation between the FDA and industry.

21 [Slide]

22 With regards to harmonization and consistency, we
23 are really talking about within the agency and we would like
24 to cite CBER as the model. We have noticed that CBER
25 utilizes science as the basis for pulling together guidance

1 documents and regulations, and it is that model that we
2 would like to see carried out through the agency, which
3 currently is not.

4 We would also recommend regarding changes
5 associated with FDAMA that there be a uniform personnel
6 training program. We are finding that there are some
7 reviewers who are knowledgeable about some of these changes
8 and some that are not, and also in terms of the
9 understanding and the handling of these types of changes so
10 the industry has a consistent response from whoever they are
11 dealing with at the agency.

12 [Slide]

13 With regards to subset analysis, that is where the
14 industry and the sponsor have to provide more information
15 and, obviously, analyses with regards to age, gender, or
16 race. We would strongly recommend that there be, again, a
17 uniform and consistent acceptance of the expectation of what
18 that would look like from the industry so that there are not
19 differences between this type of analysis being provided in
20 one division versus another division. Actually, in the
21 February 11, 1998 final rule regarding this in the Federal
22 Register, we would suggest you adopt that rule because we
23 think it is a very good approach.

24 With regards to transparency, we are really
25 talking about how, again, can the industry and FDA work more

1 closely together so that we all are fully apprised of what
2 our concerns are with regards to the product that is being
3 developed.

4 Specifically again, I would like to cite CBER as
5 having a protocol that we think is very good, whereby CBER
6 actually submits a copy of the draft submission document to
7 the sponsor prior to submitting it to the advisory panel.
8 What this allows is for the sponsor to actually develop
9 responsive documents with regards to, and it also allows the
10 sponsor to develop clarifications in case there is confusion
11 or some concern that can be clarified. At times, it also
12 can improve the accuracy of the contents of that document.
13 Currently, that is not carried out agency-wide, and we think
14 that that really is a fine representation of working closely
15 so that the document that the advisory panel receives is the
16 best it possibly can be from both the FDA's side and the
17 sponsor's side.

18 Additionally, we would like to suggest in terms of
19 accountability that perhaps there be mechanisms put in place
20 in terms of more self-reviewing or self-policing mechanisms
21 such as, again, defining and developing more uniform
22 timetables agency-wide that would be adhered to. The agency
23 has been good at starting to publish performance results and
24 we would like to see that continued on a more regular basis
25 rather than perhaps periodically, but measure themselves and

1 let the public be able to scrutinize and the industry on how
2 well they are doing. It is a great form of information, as
3 well as the point I am going to get into, the expansion of
4 the ombudsman's rule.

5 [Slide]

6 It would be, we think, advantageous if the
7 ombudsman's rule could be expanded perhaps. Currently,
8 there is a preference to handle things on a center level.
9 We would really like the ombudsman's rule to be able to have
10 the jurisdiction to go agency-wide. As an industry, we
11 would like to be able to provide maybe collectively
12 concerns. As people were mentioning whose name or whose
13 name was included in certain lists -- companies often are
14 reluctant to bring a problem that they are having with a
15 particular reviewer, whether it is with management of time
16 or timetables, or whatever, for fear that there will be
17 repercussions and that somehow they will be penalized for
18 addressing this.

19 We thought that perhaps if there was a more
20 proactive position that the ombudsman's role could take in
21 terms of hosting forums on some general issues we are having
22 so the industry could collectively response. But even more
23 specifically, if the industry or the sponsor is having a
24 difficulty with a reviewer, again whether it is on policy
25 challenges or whether it is something more specific, the

1 sponsor would be able to go immediately to the ombudsman and
2 be able to raise the issue outside of the center, not that
3 it wouldn't at some point include the center but certainly
4 would raise it to a different level so they would sort of
5 have an independent third-party person to really go to and
6 feel that they could do this at any point, not that they
7 would want to make this overly burdensome and constantly go
8 without working through the issues, but really give them a
9 place where they can go to resolve this where there are no
10 repercussions for their raising these issues to help them
11 work through this.

12 Maybe another recommendation would be in terms of
13 revising the complaint review procedure. It is our
14 understanding that when a complaint is issued against a
15 particular reviewer it goes in their personnel files and no
16 one else is really aware of it. We would like to perhaps
17 suggest a mechanism where this could be raised to higher
18 visibility and scrutiny, and where there would be a
19 mechanism so that these types of complaints and issues could
20 somehow be put in a collective manner and be available to
21 the industry so people, as well as the agency, would be able
22 to see issues that may be occurring with a particular
23 reviewer, or issues in general that seem to be recurring.

24 [Slide]

25 Finally, we obviously have submitted this document

1 and we would recommend that you go through the more specific
2 aspects of this document. We want to let you know that our
3 working group is available. There are subgroups that worked
4 on these areas, and we would be glad to spend more time
5 addressing some of the concerns or specific recommendations
6 that we made in this document, and in the spirit of FDAMA,
7 we want to thank you for hosting this meeting and say that
8 we are here and available to continue the dialogue. So,
9 thank you.

10 DR. ZOON: Thank you very much. You have given us
11 a lot to consider and we appreciate that. I think the
12 thought that went into the development of such
13 recommendations will clearly be very much considered by the
14 center. So, thank you very much -- and I am sure by the
15 agency as well.

16 Are there any clarifications? Questions? Wow!
17 [Laughter]

18 Well, I would like to thank you very much, and I
19 appreciate the effort of you coming here and the work that
20 you put into this. So, thank you very much.

21 I would now like to open the floor for any
22 additional comments that anyone may wish to make, if there
23 are any. If you will raise your hand, I will recognize you,
24 and if you can identify yourself.

25

Open Microphone

1 MS. O'DAY: My name is Miriam O'day, and I am Vice
2 President of the Immune Deficiency Foundation. I do have a
3 prepared statement, if you are accepting those.

4 DR. ZOON: Yes, come up here.

5 MS. O'DAY: I would like to say that we support
6 all of the recommendations that the regulated industry has
7 made for improved communication with the agency. I would
8 also like to note that we had short notice to make a public
9 statement today, and that we will make formal comments to
10 the docket. We may do that individually, and we may also do
11 that as the Plasma Users Coalition.

12 IDF is a member of the Plasma Users Coalition,
13 along with the National Hemophilia Foundation, the Committee
14 of 10,000, and the Alpha-1 Foundation, and the Alpha-1
15 National Organization.

16 Safe products in quantities that meet the needs of
17 the affected patient population are common goals of
18 consumers, manufacturers and the FDA. The frequent plasma
19 user communities require safe products, and depend on the
20 FDA to regulate the plasma industry accordingly. However,
21 we also note that regulatory decisions cannot be made in a
22 vacuum due to the current problems with availability of
23 plasma derivative products that are essential and life-
24 sustaining for the patients that consume them.

25 Addressing product shortages and availability has

1 been difficult for patients, physicians, manufacturers and
2 regulators. During the current and ongoing shortage of
3 IGIV, the IDF was able to quantify the effects of the
4 shortage from the patient and physician perspective through
5 a survey sent to our constituents. The FDA, industry and
6 consumers were taken by surprise by the shortage of IGIV and
7 had enormous difficulty quantifying the effects of the
8 shortage.

9 It would seem that the FDA, as the regulatory
10 agency in control of lot release, recalls and withdrawals,
11 and enforcement of regulatory actions regarding GMP
12 problems, would have the ability to access information to
13 quantify and predict near-term trends. It was surprising to
14 us and others the difficult FDA had in determining
15 distribution and supply in the marketplace.

16 We would like to ask if the FDA has engaged in
17 data collection concerning supply as recommended by the HHS
18 Advisory Committee on Blood Safety and Availability in
19 April, and will an ongoing effort be made by the FDA to
20 continue to consider supply while ensuring that the
21 manufacturers are in compliance with GMPs.

22 We support the FDA's "dear doctor" letter and the
23 fact that the FDA instituted expedited IGIV lot release when
24 they became aware of the shortage. However, we would
25 recommend staggered inspections and a regulatory environment

1 that keeps an eye on supply.

2 IDF is concerned with anecdotal reports that even
3 today several fractionators are not releasing product, or
4 are releasing limited amounts of product due to activities
5 relating to addressing GMP issues. Are inspections phased
6 in and can manufacturing and lot release continue while
7 improvements are made? We recommend that the FDA remain
8 keenly aware of the small number of manufacturers currently
9 producing pooled-plasma derivatives and, in the case of the
10 Alpha-1 community that they are serviced by a sole supplier.

11 The shortages have highlighted a need for
12 community outreach which is a difficult challenge. The FDA
13 Office of Consumer Affairs could manage solutions to patient
14 and physician outreach and coordination of information. We
15 would like to encourage OCA to work in conjunction with CBER
16 in the arena of plasma derivatives. The American public
17 feels invested in blood safety and media reports are often
18 misleading when dealing with scientific stories. Media
19 events occur which affect the products regulated by CBER and
20 the American public at large. As an example I would use the
21 outbreak of stories linking mad cow disease to CJD. OCA
22 could be the agency positioned to give public responses much
23 in the same way that they handled the situation with breast
24 implants.

25 Oftentimes consumer advocacy groups reach out to

1 Congress or the White House if they feel the governmental
2 agency they are dealing with is unresponsive. Ultimately
3 the original agency of complaint falls under undue scrutiny
4 as the result of advocacy efforts, rather than responding
5 appropriately to the original concern. To address this type
6 of issue, the NIH is establishing a public liaison office to
7 listen and respond to constituencies. The new NIH office
8 will be a repository of information equipped with the
9 ability to respond to concerns with information on existing
10 programs.

11 IDF endorses advisory committees with consumer
12 representatives as an essential component in the FDA
13 regulatory process, and we support continued use of consumer
14 advisors. We applaud the reduction of paperwork suggested
15 in the FDAMA plan, and specifically commend the institution
16 of BLAs.

17 We would further recommend that the FDA improve
18 internal communications to assist companies designing
19 clinical trial study protocols for products already on the
20 marketplace. We have heard from biotechnology companies
21 that established study parameters are often open-ended and
22 guidance from the FDA would expedite the review process.

23 In closing, any recommendations or complaints that
24 consumers may have need to be placed in the context of the
25 FDA operating with diminished resources. It is unacceptable

1 to us that the regulatory body responsible for ensuring
2 safety in the plasma industry should be operating without
3 the necessary staff. Consumer groups like ours consider FDA
4 budget constraints devastating, and will continue to urge
5 Congress to adapt increased FDA budgets.

6 Thank you.

7 DR. ZOON: Thank you very much. Are there any
8 clarifications, questions? If not, thank you. Any other
9 comments? Please identify yourself.

10 MR. WALSH: John Walsh, President of Alpha-1
11 Foundation and also a founding member of the Plasma Users
12 Coalition, and a blood derivative consumer with weekly
13 infusion of alpha-1 antiprotease inhibitor product called
14 prolantin.

15 Firstly, I am even later than Miriam with respect
16 to notification of this meeting. So, I don't have a
17 prepared statement but we will certainly add to the docket a
18 more formal statement, both from the Plasma Users Coalition
19 as well as Alpha-1 Foundation.

20 I would like to start with a kudos for the FDA
21 including, you know, open door policy. I think at CBER
22 especially we have experienced ongoing or increasingly more
23 interest by Drs. Feigal, Epstein, Weinstein, as well as you,
24 Dr. Zoon, and we appreciate that.

25 The Internet access has helped us a lot to

1 understand the process and how we can input better.
2 Specifically, the information on the Internet for this
3 meeting was very helpful. We downloaded it and read it on
4 the way to the plane.

5 [Laughter]

6 Your support for the notification of withdrawals
7 and recalls was very helpful. I think as everybody in this
8 room understands, the IPPIA, Novartis and Red Cross have
9 joined forces with consumer groups to be able to support a
10 national notification plan. We ask that the FDA make
11 certain that that is implemented to the extent that you can,
12 and again we appreciate the partnership established between
13 community, government and consumer groups.

14 The advisory committee role is critical not only
15 to exchange information but to have continued input from the
16 consumer perspective. A lot of the times we are the last
17 ones on the bus, and we are certainly the most seriously
18 affected. We expect to have an opportunity to present our
19 positions, and we appreciate our positions on the advisory
20 committees and, hopefully, FDA will have an advantage from
21 that recommendation.

22 Access to scientific resources -- advisory
23 committees are certainly one part of that. Each of our
24 organizations in the Plasma Users Coalition also has our own
25 MASACs, medical and scientific advisory committees, that

1 have made recommendations with respect to current clinical
2 trial evaluations or review and other issues related to
3 product development for our communities. We would ask that
4 you use those resources. They are open and available to you
5 at no cost, and we would ask that you use those.

6 Shortage strategies -- I haven't heard anybody
7 talk about shortages. I know there is a dilemma with the
8 FDA as to how much control you have over how much product
9 the industry manufactures. We, as a consumer community,
10 certainly ask you to address that and try to understand the
11 impact of a consent decree or warning letter as it relates
12 to supply of product. We have had instances in both the
13 IGIV communities and the alpha-1 community over the last few
14 months that have been highly publicized that have affected
15 us with life-saving therapies.

16 Right now we have a current shortage of alpha-1
17 protease inhibitor in the form of prolastin -- one
18 manufacturer, as Miriam indicated, and we have INDs by
19 companies being reviewed by FDA, and a very strong statement
20 that BPAC as well as the Advisory Committee on Blood Safety
21 and Availability, which I participate on, recommending that
22 availability be the balance, and the focus, and the
23 priority. Yet, it is understood by us -- I know we can't
24 discuss IND details, and we don't have access to details,
25 that they are requiring use of 1 kilo of a product that is

1 in short supply, and we will have allocation until another
2 product comes on the market, or an IND request for product
3 evaluation. One kilo of product out of a patient community
4 that is only getting 50 percent, just increased in August to
5 80 percent of what we need to infuse on a weekly basis makes
6 no sense to us. It is going to detract from the current
7 supply available. So, we ask that that be considered so you
8 are more sensitive to the IND process, and listen to our
9 needs, if you will.

10 That is all I have to say. I have a lot more to
11 say but I just brought some notes down. We appreciate the
12 opportunity to present in an open forum. We will welcome
13 participation, and want very much to give input to the FDA.
14 Thank you for the forum.

15 DR. ZOON: Thank you very much. Are there any
16 other comments, statements, questions?

17 MS. SCOTT: Amy Scott, from Smith Kline-Beecham.
18 Kathy asked me to please make a comment. So, I will.

19 Actually, I have been thinking all morning after
20 hearing everybody talk about the different ways to get more
21 communication going between the agency and the industry.
22 There have been a lot of proposals made for a lot of formal
23 type of situations with quarterly meetings, and things like
24 that.

25 I would like to bring it down just to the level of

1 the review process, and remind everybody that one of the
2 great strengths, I think, of CBER as a regulatory body has
3 been the ability to collaborate with the industry, and to
4 work through the review process together, and have very
5 open, maybe less formal communication throughout the review
6 process.

7 I think part of the problems of all of the
8 additional pressures that are being put on the agency at
9 this point is that there is a concern in the industry and
10 probably among yourself also that that is going to go away,
11 that things are going to become more formalized. So, I
12 would encourage the folks at the agency to figure out ways
13 to preserve that type of an approach to the regulatory
14 process because I think it is very important and it really
15 does help to facilitate things in the long run.

16 I jotted down a few ideas while I was sitting
17 there about the ways that you might internally think of
18 preserving this. One of the things is to just make sure
19 that your reviewers and your staff, especially the newer
20 folks, really understand the importance of that type of open
21 communication and how it really can facilitate things in the
22 end.

23 Somebody from the Massachusetts Biotechnical
24 Council mentioned the need for training of the folks on your
25 staff, especially in terms of all this regulatory reform and

1 the Modernization Act and all of the initiatives that are
2 taking place to make sure that they are not only aware of
3 these things, but they really understand the implications of
4 these things so that when industry comes to them to use
5 particular tools that are being afforded and they really
6 know how to work through those, and use those tools.

7 I think also it might be useful for the industry
8 if you could think about it and give us some helpful hints
9 or some guidance on how you see we could help you preserve
10 that type of collaborative interaction; what we can do as a
11 company or as an industry to give you better heads-up on
12 questions and issues that we might find necessary to discuss
13 so that you could then get back to us and give us feedback
14 in a timely fashion.

15 Also, I think with so much that is happening with
16 all this regulatory reform, one of the big concerns is the
17 logistical aspects of it all. So, that is another reason to
18 maintain this open communication so that the industry can
19 call and talk to you about, "gosh, how do we do this? how do
20 we do that?" If there are decisions that come out of some
21 of this back and forth logistical discussion that aren't
22 necessarily in a guidance document or aren't in the
23 regulations, if you make a decision for a particular company
24 that is then a generic type decision that could be applied
25 to other situations that other companies may have, that you

1 go ahead and communicate that in maybe a policy memorandum
2 or something like that as just kind of building upon the
3 guidance documents that exist, without having to go through
4 all sorts of other formal processes for getting documents
5 out there.

6 So, those are just some thoughts.

7 DR. ZOON: Thank you very much. Are there any
8 other comments? Yes?

9 MR. KLAMRZYNSKI: Matt Klamrzynski, Abbott
10 Laboratories. I have submitted submissions over the last 15
11 years to CBER, and the notable points that have been made
12 here in trying to implement FDAMA are all very good. The
13 one that I just wanted to focus on now is in support of the
14 last speaker and also MBC on the highly interactive process
15 that is necessary to help CBER meet their mission of
16 enhancing public health by bringing new, innovative products
17 to the marketplace and to patients.

18 What enhances it the most in industry is to have
19 as much feedback as possible from CBER in the earliest time
20 frame because many of the questions that are generated will
21 result in long-term experiments or clinical trials. That is
22 why the predetermination meetings and the agreement meetings
23 are going to be very, very significant to industry.
24 Guidances are going to be necessary. But also during the
25 review process itself, you have set up a very professional,

1 business-like management review process over the years, but
2 we have to make it work better and in a more timely fashion.
3 And, I think the guidances and the working groups that maybe
4 come out of these meetings will help in that regard.

5 Thank you.

6 DR. ZOON: Thank you very much. Any other
7 additional comments?

8 MR. ELEGOLD: Since I am supposed to be the
9 operational guy, can I ask the last four speakers, before
10 you leave to stop over at this table and give the
11 transcriber and the minute-taker the names and affiliations
12 just so when we get the transcript out they will appear
13 correctly? Thank you.

14 MR. WALSH: I don't mean to belabor it but I have
15 one more issue with respect to shortages. We have
16 cooperated extensively with CBER with respect to the
17 prolactin shortage, and in the immediate exchange, when we
18 determined from patients in Germany and clinicians in
19 Germany that there was a shortage of prolactin, we asked
20 CBER for information on that. Once they determined exactly
21 what the problem was, they were forthcoming and cooperative.
22 In the meantime, the leadership of our community agreed to
23 basically discourage calls into the Office of Compliance
24 regarding shortage issues. In the process, over the last
25 few months, in three different testimonies before Congress,

1 the BPAC and the HHS Advisory Committee on Blood Safety and
2 Availability, the FDA reported that because of the decrease
3 in calls, that must correlate to a decrease in the shortage
4 situation, and that is just not true.

5 We need to work out a system. Right now, if I
6 call the Office of Compliance, inevitably what they will
7 tell me is that there is not a prolactin shortage. Well,
8 Bayer is never going to be able to satisfy demand. Our
9 community is always going to have a shortage and will
10 effectively be on allocation because over 400 to 600 people
11 can't get product that need product until another
12 manufacturer comes on line. So, we need to work a system
13 out whether, as Miriam said, it is to change it over to
14 consumer affairs or whether it is to say to the FDA we can't
15 comment because we don't have any control, but we need as
16 accurate information as possible. If CBER's measure of a
17 shortage is call-ins, then we can give you call-ins.

18 [Laughter]

19 But that is counter-productive and we understand
20 that. So, we need to work out a system, whether it is to
21 get a working group together to do that or not, that should
22 be considered in a shortage and allocation strategy.

23 DR. ZOON: Thank you very much. Any other
24 comments or issues? Don't be shy!

25 I want to thank all the speakers today, both the

1 formal and informal speakers, for their well thought out
2 comments, and we appreciate them, and also look forward very
3 much to the written comments to the docket. Many of the
4 ideas presented are very, very worthwhile and good. Some of
5 these we will implement as soon as possible because it just
6 makes so much sense to do so. So, I think just based on
7 what we heard today, we will do some things relatively
8 quickly.

9 The docket will remain open and available for your
10 review and comment, and don't forget the meeting, August
11 28th, in Oakland and the overall FDA meeting which is
12 scheduled in mid-September.

13 I want to thank you for CBER and, Linda, would you
14 like to make any last comments for the agency?

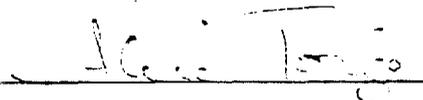
15 MS. SUYDAM: Well, I thank you all also. It was a
16 very productive meeting and it was what we had hoped these
17 meetings would be. I think if this is a sign of what the
18 rest are going to be like, I am very encouraged about this
19 process.

20 DR. ZOON: Thank you. Thank you all.

21 - [Whereupon, at 12:20 p.m., the proceedings were
22 adjourned]

C E R T I F I C A T E

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



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