DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

TEAM BIOLOGICS PUBLIC MEETING

Wednesday, May 21, 2003

8:10 a.m.

Parklawn Conference Center/Room D
Parklawn Building
5100 Fishers Lane
Rockville, Maryland

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C O N T E N T S

Presentations

P R O C E E D I N G S

Opening Remarks

MS. WHELAN: I would like to welcome you. There will be transcripts available of this meeting approximately two weeks or so after and we will have them posted on the CBER website as well as the ORA website.

Without further time-wasters, I am going to go ahead and introduce Anne Johnson who will be moderating the meeting.

Moderator

MS. JOHNSON: I would also like to welcome each and every one of you to today's public meeting. Before we get started, would you stand up and introduce yourselves. Also, the folks here at the head table. After that, we are going to give you a chance to briefly introduce yourselves just by name and organization.

Let's start with the folks at the head table.

MR. BOWERS: I am Lee Bowers. I am District Director in Baltimore.

MS. GUSTAFSON: I am Mary Gustafson. I am Senior Director, Global Regulatory Policy for Plasma Protein Therapeutics Association.

MR. MADSEN: I am Russ Madsen. I am Senior Vice President, Science and Technology, for PDA.

[Attendee Introductions.]

MS. JOHNSON: Thank you. I am Anne Johnson. I am a compliance officer in ORA's Office of Enforcement. It is a pleasure to have you all here. We are looking forward to your comments, suggestions and points to consider. We strongly encourage frank back-and-forth on the issues at hand today.

Without further delay, I am going to introduce Lee Bowers as our first speaker this morning. Lee is a District Director in FDA's Baltimore District Office. He is going to give us additional words of welcome as well as introducing us to today's meeting.

Welcome and Introduction

MR. BOWERS: Good morning to you all. I thank you for coming today. I was a little surprised at the paucity of attendees or registrants from the industry. My history working with biological products has kind of led me to believe that there was not much shyness on the part of industry or people who were involved in biologics. I hope this is not an indication that you all have suddenly gotten shy, or maybe I am being a little optimistic.

But, certainly, your comments are welcome here today. FDA is coming into this with an open mind. We are soliciting your comments. We need your help and I

think that you can prove to be valuable in determining how we are going to evaluate team biologics.

We also want to hear about your experiences with that group. Like I say, this is your opportunity. I believe the docket may still be open for those of you who have not responded. Is that right, Jackie? It is still open until June 10, so you are certainly welcome to send in your comments to that.

What I am going to do today is give you a brief outline of the history of team biologics and its implementation. We want to discuss a little bit of FDA's Pharmaceutical cGMPs for the Twenty First Century Initiative, how that is affecting team biologics right now and how it will affect team biologics in the future and then talk about the focus of today's public meeting.

Team biologics is a relatively new program for FDA. It was initiated in 1997 due to some reports by the General Accounting Office, Blood Safety, FDA Oversight and Remaining Issues of Safety, which was published in 1997. And then another review by the Office of Inspector General from HHS which was entitled A Review of FDA's Inspection Process of Plasma Fractionators which was published in June of 1997.

Both reports were somewhat critical of FDA and contained recommendations on how they believe we could

improve our inspectional process with relation to blood, blood products and plasma manufacturers. That was pretty much the limit of the reports.

FDA, as we often do when we get a criticism, broadened that scope and decided to include all biological products in a new approach called Team Biologics; A Plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries. That sounds like a Federal Register Announcement title to me.

What we wanted to do, though, was to improve consistency not only within the FDA district offices and the field but between our actions with industry from CBER and the field. We wanted to increase the timeliness of our response which has always been something that industry has been critical of, and we have been internally critical of that, too and we wanted to assure more consistency of our policies, our guidelines and our regulations.

So we got started with team biologics after the publication of the Implementation Plan and began, in October of 1997, basically four months after the OIG report was published, added licensed in vitro diagnostic products in April of '98, the biotechnology and allergenic products in October of 1998, and the vaccines

and the other various products in October of 1999 which completed basically the core team activities of team biologics.

What FDA did when we received the reports is we got a workgroup together and developed an implementation plan for team biologics. That consisted of an operations group and a steering committee. The operations group was charged primarily with assuring the policy was consistent, and that sort of thing, to resolve problems that were occurring between CBER and the field.

That operations group still does meet. I guess one of the reasons I am here is I am Co-Chair of that group now. But the goals of the process were to assure a comprehensive regulatory posture among all product lines, both blood and the regulated industry with vaccines, allergenics and that sort of thing; promote uniformity between CBER and the field and among the field components associated with inspections, policy, implementation and cGMP interpretation.

There had been some complaints that different districts were handing different investigational operations in different ways and possibly even we were formulating a regulatory plan for a particular firm. Different firms in different areas were being treated differently.

Finally, we wanted to develop and maintain a highly and professional trained workforce.

In addition, we wanted to design and organize an approach to inspections that clearly defined both the ORA field and the CBER roles. You have to remember that, before team biologics, while the field was primarily involved in doing the blood and plasma inspections, the field was not involved, particularly, in the vaccines, the fractionated products, the allergens, those products covered by the core team.

As they were transferred over to the field, obviously, there were some issues we had to get over, some problems we had to resolve and that was part of the reason that we wanted, when we implemented team biologics, the operations group was set up.

We wanted to design a rapid and effective process for resolving ORA and CBER differences. That has worked somewhat. Sometimes, it is rapid. Sometimes it is not. I think that, in the time I have been associated with the team biologics, and that has been just three years, we have done a much better job in resolving those differences and ironed out problems.

I wanted to focus on operation, on policy approach, that fits FDA's existing structures and systems. However, you need to understand that the team-

biologics approach was totally different than anything that FDA had done in the past. What we had done with the blood and the blood products and plasma was left the responsibility for the investigations in the field in the district offices.

However, what we did is, with training, we had a specific number of blood-bank investigators that went through extensive training, both advanced and basic blood-bank. Then we also trained our compliance officer and the supervisor in each district to deal with those investigators. That is not typical in normal programs in FDA.

With the core team, that was totally different than anything we have done in the past. What we did was we established twelve to sixteen investigators that were located in the district but managed by ORA headquarters. There were up to four compliance officers.

In ORA, there were also four compliance officers. They were managed by Office of Enforcement in ORA. There were CBER compliance officers attached to that and then the CBER product specialists which were managed in the CBER Program Offices.

The idea was that the product specialist, the ORA investigators and the compliance officers in both CBER and ORA would work together from the very beginning

of an inspectional process to facilitate that process and assure consistency. So that is something that was totally different. It is something that, now that we are moving into the cGMP initiative that is being explored, a similar type but no exactly the same, process for drugs.

In furthering the consistency or the working in a consistent manner in the field, in the core-team activities, the operations group developed two SOPs, one for compliance assessment and one for the inspectional process. Those have been in use in the field and in CBER for approximately two years, now.

We wanted to provide oversight and assurances of consistent quality of work products for decisions and/or actions. That was primarily the role of the operations group and the steering committee. We wanted to bring about maximum efficiency of operations. That was the reason for concentrating the investigational activities in a smaller number of investigators than is typically handled in other program areas, and we wanted to evaluate new methods for implementing the biologic inspection and enforcement programs.

All of this was in an effort, for the agency--we wanted to be innovative. We wanted to be consistent. Certainly we wanted to promote the availability of safe products.

The pharmaceutical cGMP initiative is a risk-based approach that began in August of 2002. It is part of a program that Secretary Tommy Thompson in HHS initiated to assure safe and abundant medical care of the American public. It says here it is a two-year program but, as a result of a meeting we had last April with pharmaceutical industry, we have all realized it is going to be much more than a two-year program. But we have got some initial goals and time lines that we need to meet in a two-year program which should get this moving right along.

It applies to all pharmaceuticals including biological, human drugs, veterinary drugs. However, it does exclude the blood and plasma.

The objectives of this initiative are to insure regulatory review and inspection policies that are based on state-of-the-art pharmaceutical science and encourage adoption of new technological advances by the pharmaceutical industry. This is primarily in response to some suggestions by the industry that FDA was inhibiting progress in development of new ways of doing things. The cGMPs may be a little out of date--they are some thirty years old--and that there were different ways that we could regulate industry in a more--a manner where we work together rather than in confrontation.

Again, the cGMP initiative sets out to clear up inconsistencies that may be occurring not only among the field offices, in the different district offices, but also among the centers, the Center for Veterinary Medicine, Biologics and in Drugs.

Other objectives are to integrate advances in quality-management techniques including quality systems and approaches into the agency's regulatory standards and systems for review of inspection and process.

That is something that the field has embarked on probably about a year ago. The districts are in various stages of a quality-management system, developing that. It is being led by ORA Headquarters but some of the regions went out on their own and developed their own quality-management systems. There are in various stages of development right now.

It is something that is moving on into the Centers, I believe, at a pretty rapid pace. We wanted to implement risk-based approaches to our investigational and our review activities and enhance the consistency and coordination of the agency drug-quality programs.

I mentioned the April workshop that was co-sponsored by FDA and PQRI, the Product Quality Research Institute. That was a two-and-a-half-day meeting where we discussed a variety of these issues. Industry was

asked for input, similar to what you are being asked for today, to help FDA become more effective, become more innovative and to have a better approach in working with industry rather than opposed to industry.

Think that the general comments from that workshop were industry was extremely delighted to be there. They were happy for the opportunity. I think the interesting thing is some of the suggestions that were made at that meeting were things that FDA had come up with and meshed hand-in-hand with those that we had been working on for the previous six months, since August.

So I think that was a good indication that industry and FDA are kind of on the same page and that we are interested in working together.

One of the things that I think most impressed me about that meeting was the admission by both industry and FDA that there is some risk involved in this. This is going to require a more open, more honest, more trusting stance on both of our parts. There was a great deal of discussion who was going to start that process. I think that the consensus was that the process has got to start with both of us. I think that is where we are headed.

Some of the things that kind of overflow from the cGMP initiative but the were also being worked on by the team-biologics operations group prior to the cGMP

initiative were the adoption of an internal quality-management system. The operations group had set up a workgroup to work on that back in January of 2002 and that process is continuing.

The development of metrics to determine the industry of team biologics. That is really the focus that we are here today for. That workgroup tried to make some stabs in an evaluation. Frankly, what we found is the data we have, while it is traditional data that FDA maintains, it is probably not the most effective way to assess team biologics, the industry and the safety of products.

We want to standardize the training and qualifications of core-team members. That is another workgroup. Some of the initiatives they have come up with is having the--of course, the investigators in the field have always been going through the OR University plan but one of the things we are working on now is to have some of the CBER product specialists participate in that training program, possibly not all aspects of it but certain aspects of it, so that they are able to work better with the field investigators.

We are also going to train the field investigators in some of the areas where the CBER product specialists are trained. We wanted risk-based work

planning. In other words, we wanted to plan our inspections, not that we needed to do a certain number of firms every single year but that we had to do a certain number of firms based on the risk of those products.

That would mean that some firms, some industries, would be inspected more often. Some would be inspected less often. Finally, we wanted to increase communications between Headquarters and the fields. We have done quite a few things on that. At this point, we have monthly conference calls between the product specialists, the field investigators and the compliance officers. They discuss it there. There are a variety of issues that need clearing up or that we think that more information is needed.

We are asking you for your input on performing this evaluation. We want to do a prospective evaluation of team biologics. We want to know where we should be doing, what types of measures we should be doing in the future. I think that industry has a lot of that information.

I think that your ideas on how to evaluate the program will probably lead to a much better evaluation rather than FDA measuring its effectiveness by the number of recalls, the number of injunctions, the number of warning letters, the number of inspections. That is the

kind of data we have readily available and I don't think it is really what we want to use for an evaluation of this program.

The criteria that we are asking you to address today is industry compliance with applicable laws and regulations. We want your input on that. The consistency of our inspection and compliance activities. This is your opportunity. I know at the cGMP workshop in April, there were quite a few comments about the team-biologics approach and I ask you not to be shy today.

We want to hear about the effects of our inspection and compliance activities on product quality and, finally, the impact of the team-biologics approach on public health.

The next series of slides will provide some additional information on each of these four items we are asking you to comment on.

For each item, we are asking you to give us input about specific methods, tools, criteria and metrics that you think the agency should use to measure the effectiveness of team biologics. I think that, in the past in my career, I have been involved in some evaluations of FDA programs. What we have pretty much done is a traditional approach. We have measured our regulatory actions. We have measured recalls. We have

measured samples collected. We have measured violative samples.

Basically, that gives you an evaluation of what FDA has done but I don't think it goes to the heart of the matter of what exactly is the quality, the status of industry in the United States. So that is why we are asking you to help us on this.

We asking the approach to take in measuring industry compliance to include the types of methods or tools you would use in your evaluation if you were to evaluate team biologics or if you were to evaluate the quality of a particular product that you are involved with. We are asking for the criteria you would use to assess the effectiveness of team biologics in achieving industry compliance.

The team approach has been in effect now for about four or five years. I think most of you in industry have had a pretty good experience with it, or at least ample time to experience it. Whether it has been good or not is probably dependent on how you look at it.

But you may suggest that the team-biologic approach has served its course and we need to move onto something else. We are open to that. You are welcome to provide your comments.

We are asking for the approach you would take in measuring industry compliance including the types of tools you would use for the evaluation. Many firms, I know, evaluate their processes. They evaluate their product quality. Those may be applicable to the team-biologics approach, what we had, as we move into this Twenty First Century with the regulation of these products, and, finally, the criteria you would use to assess the effectiveness of team biologics in achieving industry compliance.

Obviously, we are all in this together. Regulatory actions against firms do not serve FDA well. They do not serve you well. They do not assure consistent product quality. They do not assure consistent amount of product. We need to work on that together.

We are asking you how to assess the programs inspection approach regarding the scope and depth of the systems and the product coverage. We have moved in ORA in some areas to try to do abbreviated inspections, to get into firms faster and get out faster if there is no indication of problems.

I know that the core-team activities, particularly, those inspections are often long. There are possibilities to abbreviate those. We are working

right now in the blood and blood-products area on streamlining that program. That is one of the first steps we are going to do. Then, after we do that, we are going to look at some of the other programs and that would include the core-team compliance programs.

We are asking for your scientific and regulatory knowledge, your skills that you perceive of our inspectional personnel. I heard at the April meeting some comments that the team-biologics inspectors, firms felt that they were providing training for those inspectors and that was really not their responsibility.

I would comment on that that it is quite interesting. In the time period that I have been involved with team biologics, most of the investigators that we have lost or that have left the agency have gone on to industry and I would wonder if, in fact, industry is providing all the training for these people, why they would be hiring them again. But that is just my perception of that.

Finally, the length and frequency of the inspections. I know there are a lot of comments on that.

We are asking for your views and your experiences with post-inspection outcomes; for example, the timeliness of our post-inspection of correspondence, our administrative and legal actions or regulatory

meetings, et cetera, in the context of evaluating the consistency of the outcomes.

I think that, in the core-team activities, we have got a pretty good handle since we have got a very small number of compliance officers, a very small number of investigators, and they are all handled at a centralized headquarters office rather than in twenty districts. So I think that is probably fairly consistent but, again, we need your input on that.

You are on the receiving end of this and I think you are the ones that are in the best positive to give us a really open and honest assessment of that. We certainly want to assess the fairness of the outcomes of our inspections and our regulatory activities.

Finally, the last approach, and this is something that we, again, talked about during the two-and-a-half-day April workshop, how to define product quality. I think that is something that seems very simple on the surface but I remember, in some of the workgroups, we worked for three or four hours just on that particular aspect, what is product quality, what does it mean, how do we achieve it.

Approaches that you would use to assess the impact of product quality. Finally, discussion of the

scope of deviations from the cGMPs that should trigger a product-quality assessment.

These are all things that I think industry is in a very good position to determine. I am suggesting that you, by being at this meeting and by your input and your contributions here, can make a difference in how FDA regulates the biologics industry in the future. We are open to your suggestions and we hope you will take us up on that.

Finally, what criteria would you consider in assessing the program's impact on product safety and product availability. Obviously, those are two issues that weigh heavily on FDA and on industry. It is no good to have a good inspectorate, a well-trained inspectorate, in FDA that shuts down industry where there is no product available. That is not what FDA is about and it is certainly not what you all are about. So, we are looking for some criteria that you would use to guide us in assessing that.

Finally, in closing, your comments and suggestions are going to be used. They are going to be listened to. They are going to be reviewed. They are going to be talked about. They will serve as an invaluable resource in assisting us in accomplishing our objectives and providing criteria to design an evaluation

plan to prospectively evaluate the effectiveness of the team-biologics program.

Whether team biologics lives or dies can depend on this and your comments can have a sincere effect on that. We need input from you, from consumers. We don't profess to know it all. So, again, I am pleading with you to speak out and comment.

Again, these comments are going to be used in part to the greater cGMP Initiative, to modernize our regulatory approach toward drug manufacturing and product quality. Team biologics is still operating a little bit separately from the cGMP Initiative but there are a lot of interfaces. There are a lot of meetings that are held between the Initiative Workgroup. In fact, we are having one tomorrow with some of the CDER people at our operations group meeting to discuss interactions and how we can be more consistent among the two approaches.

Finally, we introduced earlier the team-biologics public meeting coordination team. I think they did a good job. We planned on having this meeting--we only thought about having this meeting about six weeks ago. Jackie Little and her group did, I think, an excellent job in getting this together, securing a room, working with you all to, hopefully, make this an effective and a valuable meeting for all of you.

With that, I thank you.

MS. JOHNSON: Thank you, Lee.

We will now move on to the next segment of our program where we, the FDA, get the opportunity to hear from you. We have four planned presentations. We are going to hear from representatives of the Plasma Protein Therapeutics Association, the Parenteral Drug Association, the National Hemophilia Foundation and, finally, the Immune Deficiency Foundation, in that order.

Each individual session or presentation is going to be followed by a Q&A session. Initially, we will open that up to the workgroup committee members. They are seated here at the head table. After they are finished with their questions or comments, we will then open it up to everyone here in attendance today.

With that, I will introduce our first speaker, Mary Gustafson, Senior Director, Global Regulatory Policy, representing the Plasma Protein Therapeutics Association.

Presentations

Plasma Protein Therapeutics Association (PPTA)

MS. GUSTAFSON: On behalf of the Association, I would like to thank you for providing the public forum to solicit views and comments to assist you in evaluating the effectiveness of the Team Biologics Program.

PPTA is a global association that advocates for the world's leading source-plasma collectors and producers of plasma-based and recombinant biological therapeutics. The medicines produced by PPTA members are used in treating life-threatening diseases and serious medical conditions including bleeding disorders, immune-system deficiencies, alpha-1 antitrypsin deficiencies, burns and shocks.

Safety is the number-one priority for the members of PPTA. In furtherance of safety and quality, PPTA sponsors programs of voluntary-standard initiatives for both its collectors and final-produce manufacturers. The International Quality Plasma Program, the IQPP, for collectors and the quality, safety, excellence, assurance and leadership, or Q-SEAL Program, for fractionators set standards beyond current cGMPs that are verified by independent auditors.

As part of an overall quality system, PPTA members welcome oversight by the Food and Drug Administration. In 1997, FDA initiated team biologics, as Mr. Bowers said, to focus FDA's regulatory oversight of biological products. At that time, FDA's Office of Regulatory Affairs and Center for Biologics Evaluation and Research entered together to better address the continued quality and safety of biological products,

resolve inconsistencies and bring products into compliance.

The original goals of the program were on Mr. Bower's slide, so I won't go over those again. However, we feel that the goals from 1997 are relevant today and that any program that is developed for measuring the effectiveness of the program should include success in meeting these original goals.

In preparing for today's presentation, presenters were asked to provide input in four areas of assessing the effectiveness of team biologics. These areas include industry compliance, consistency of inspection and compliance activities and effects on product quality and impact on the public health.

In terms of assessing industry compliance with applicable laws and regulations, we asked our member companies and we came up with the metrics that Mr. Bowers had said that are readily available but that may not be the right metrics for evaluating the program.

These are the recall seizures, license suspensions and revocations, warning letters and injunctions, the traditional, I guess, numbers. It is with great trepidation that I even put these up on a slide because I have been around long enough that I

remember when investigators were actually rewarded for the number of these actions that they initiated.

We do not want to go back to that at all. I don't think you do, either. I think the goal should be to promote voluntary compliance of the industry. As Mr. Bowers mentioned, no one wins when there is a regulatory action. It undermines public confidence and the confidence in the people who depend on our medications.

Also a goal is to increase to agency efficiency. I think the agency is getting a lot better at managing injunctions because there have been so many of them, but they are still extreme resource burners. In the end, I don't know that they do anyone a lot of good. I know that sometimes they are necessary.

But I guess, in terms of metrics, one thing that probably hasn't been around a long time for this group of industry is the Biological Product Deviation Reports. The regulation was changed in the last couple of years and there is increased reporting. I know that there are reports that go out, compilations of these BPDRs, but we would like for the agency to take this a step further and really use the BPDR reporting system as a system for continuous improvement in the industry.

In terms of the second item that we were to discuss, determining the consistency of inspection and

compliance activities, we thought of some of the tools that could be used. One of them would be customer-feedback surveys. You can't have your car repaired, you can't go to the dentist, you can't have a plumber come to your house, without having a telephone call or a survey sent to your house or one dropped off that says, "How are we doing?" Sometimes they are very short. Sometimes they are very long and detailed survey tools.

I actually saw a cartoon the other day, the Nonsequitor. It showed this little gal out in the field with a bunch of sheep. She is holding a sign, and it says, "How am I herding? Call 1-800-Bo-Peep." I wasn't quick enough to get the slide copied for it, but it is pervasive, the customer-feedback surveys.

Obviously, I don't have a lot of insight into how to develop the surveys, but there are people who do this for a living and some of whom, I think are quite good. One reason why we think a customer feedback survey would be a good tool is it is for everyone. It would be something that everyone would be asked to fill out.

I know when manufacturers have complaints about an inspection, they are always told, "Well, give us that feedback. Everyone has a supervisor. Go up the chain of command. Call in. Write in."

But there is a lot of fear in the industry of doing that and the "R" word comes up that we don't want to talk about, retribution, retaliation. Manufacturers are always assured that this will not happen, does not happen, will not be tolerated. But yet there is a fear in the industry to pick up that telephone or to write an individual letter.

A customer-feedback survey that would be sent to everybody I think would neutralize that fear because the expectation would be that you will participate and you will provide feedback and it will be used, then, to improve the system.

Another item would be peer review. I didn't think of this myself. I saw it in one of the sheets. I think Bruce Burlington had mentioned this in a talk that he had given to Temple University. But, yes, having the other members of the team review the inspection reports and the work preps, the timeliness, the number of deficiencies, the 483s and provide feedback in, hopefully, a nonconfrontational environment because I think your peers are the ones who can actually help you and help the program improve.

And then we have management review. With the core-team management, this may already be happening, but I know that the inspections are signed off by

supervisors. However, is there a review of the inspections or the recommended compliance actions, then, in terms of the aggregate, looking at them across the board for consistency and really using this information, then, to go back and improve the program.

I think that the goals of using these tools would be to have a consistent scope and depth of the inspections across the industry, to insure that there are appropriate knowledge, skills and professionalism in the work force and to make sure that there is an even application of agency rules and policies.

In terms of determining the effects of the program on product quality, we again have the metrics that are used for product quality. Those are recalls and seizures. We can also use the Biological Deviation Reporting System, again, as a quality-improvement tool by looking at the number and the types of the BPDRs and the true impact on product quality.

I think the Internal Product Complaint Files of the manufacturers are a great tool because, when it comes right down to it, customer satisfaction is what determines our product quality.

The goal, again, should be to effect process improvements and to better relate GMP observations to product quality. I think this is really, really tough

because of just what GMPs are. It is kind of an early warning system. It doesn't tell you that there are actual product-quality problems. However, it tells you that the conditions exist for having a catastrophe.

But we need a better way to really review and to look at the GMP issues and to tie those into product quality. Again, this is not an easy thing. If it were easy, it would have been done a long time ago.

In terms of assessing the impact of the team biologics on public health, I think, again, metrics would be the review of the 483s and to look at those in terms of whether they are noting system problems within a company or isolated observations. I think it is very hard for the public to make this determination. The 483 is a very, very powerful document.

It is released to the public before the ink is even dry. So there should be great care that goes into listing observations on a 483 because of the impact or the perception of those 483 items. Personally, I hate to look at the stand-alone 483. Maybe it is because I grew up in compliance, but I want to see the background. I want to see the report. I want to see the documentation. I want to see exactly what backed up that 483 observation.

I think that is one of the defects of having the 483s releasable immediately is that you don't have that background. By all means, the public doesn't have the background. So they are kind of scary.

Then there should be some risk/benefit analysis done. I think, again, we have got the Twenty First Century. I think that is being done but pay particular attention to the risk of, say, 483 items or the risk of a GMP observation versus the benefit.

I think the goals of this should be to better understand the science and the use of the product. In that, I was very, very glad to hear that, in the training that product specialists are being brought in and, also, that there is the monthly conference calls. I think that is terrific. I think it will go a long way to helping the product specialists understand the inspection needs and having the inspectors understand the science behind the products and the use of the products.

Again, the FDA goals should be to focus on consumer protection.

In summary, again, we would like to commend ORA and CBER for seeking input from the public. We think that this is very valuable and don't be discouraged by the limited participation. I think that this is a first step. I don't think many of us--we looked at the four

areas. We looked at what was expected and, perhaps, didn't really quite understand or appreciate the scope of it.

I think it should be a first step to encourage public input. I think it also shows that you recognize that better oversight of the program is needed. There are anecdotal reports. I know, by trying to focus in the four areas and asking for metrics, that you want to go beyond anecdotes, and I think we do, too.

I was real happy to hear Mr. Bowers say that you want to partner with industry in terms of having a less adversarial relationship. I think one way for partnering, and our company have suggested this is the past, is to use the industry in terms of training and not just training during the inspection, because that is time-consuming and it is only a one-on-one, but ask industry to come in and participate in certain training in process or in the science behind the product.

Thank you.

MS. JOHNSON: Thanks, Mary.

The floor is now open for any questions or comments from either the workgroup committee members or anyone seated here at the head table.

MS. ROSSITER: Emily Rossiter from Regulatory Resources. Is anyone else from the blood-bank sector

here today? I can't imagine why they are not. I will be in touch with them after the meeting since the docket is still open. Over half the blood collected in the U.S. is currently collected under consent decree. I hope that that fact hasn't hindered the comment process for a hearing of this type.

But I know the docket still is open so, hopefully, there will be some written comments provided. I don't have any prepared because I am not a spokesman for the three big blood-bank associations, but I can assure you there are plenty of comments out there and I think the FDA needs to hear them.

I wanted to expand just on two comments that Mary made. She talked about a feedback form. The Center for Devices, several years ago, did develop a customer-feedback form. I am not sure what it was called, but we actually adapted it for the Citings Program for our members. It is a one-page form. It has maybe four or five questions on it with a lot of fill-in-the-blank space for customers.

I think that CBER may want to look at that as a possible--and talk to CDRH about their experience with that form. I don't know if they are still using it, but we are still using it in the Citings Program.

Secondarily, the complaints system that I am sure the FDA has is another metrics area that I think could be used to track whether or not the complaints are up or down, whether the complaints are higher in a certain region of the country than another, that would help look at the big picture and detect potential areas that need more attention with team biologics.

MS. JOHNSON: Thank you.

MR. LEWIS: Richard Lewis, Office of Blood at CBER. I would like to focus on a couple of things, both in your talk and comments that Emily made. Both of you commented on the customer-feedback surveys. I wonder who you define as our customers. We recognize that our interaction is predominantly with the manufacturers but our ultimate customers are the patients that use these particular products.

How do we measure the manufacturers' output and whether the quality has improved from what is produced by manufacturers? And how do you see a customer survey addressing that?

MS. GUSTAFSON: Obviously, a customer survey, in terms of the folks of who are inspected. I was thinking in terms of the tool that would be used post-inspection, kind of a post-inspection survey. However, a couple of the presenters today are from the consumer groups, the

user groups. I think, too, that that would be valuable also, to get feedback from people who actually use our products in terms of how are we doing, because, when it comes right down to it, those are the ultimate consumers and they are the ones that we need to satisfy and we need to satisfy. We need to have safe, quality products and they needs to be accessible, and we need to have choice.

MR. LEWIS: Thanks. Then, regarding the blood industry, in our internal evaluation of team biologics, the cadre concept of having investigators from the districts, specially trained investigators, got the highest ratings of team biologics. It was felt, at least by our internal evaluation, that the program was doing a good job.

So, Emily and others, if you do take that back to them and ask for their comments to the docket, I would appreciate it.

MR. MASIELLO: Steve Masiello, CBER. Mary, you said that quality equals costumer satisfaction. Can you give us a little more insight into any information you might have in that area, what is up, what is down, changes, perhaps?

MS. GUSTAFSON: I don't really have a finger on the pulse of the customers. Perhaps, like I said, we have a couple of presenters that represent consumers but,

in general quality jargon, you end up that the ultimate quality of the product is having a satisfied customer. So I think we have to take that into account.

I think, from an FDA standpoint, we think of quality in terms of safety, purity, potency. That is right. That is quality. But, in the final analysis, it is the customer satisfaction that really counts.

MR. MUNSON: Terry Munson representing PDA, also. One other thing about using defect reports, though, is the same thing companies go through with their consumer complaints. You have to be very, very careful with that metric because you have to differentiate those complaints that are true quality-related issues as opposed to somebody misusing a product or using it in a manner that wasn't specified by the manufacturer or approved.

So you have to be really careful and that is going to require a lot of analysis, looking at the defect reports, just as manufacturers have to do with their own complaints that they receive internally is trying to make those differentiations so that you are dealing with truly defects that are quality issues, something that the manufacturer had control over and should be responding to and fixing, and those you should see as your investigations go and as those things get corrected, you

should see less and less of those. Those are the items you should be looking at.

But it is just a cautionary statement on looking at the defect reports.

MS. RISSO: Sharon Risso, Office of Therapeutics at CBER. I was just wondering, for Mary and other industry representatives, the metrics that you have talked about with respect to product quality are very visible metrics to FDA. But I am wondering if there are some other things that you, as manufacturers, look at internally; for example, number of lots reworked, failures, other types of internal deviations that are taken care of internally through your QA/QC programs that might, in fact, reflect overall operation.

Is it feasible for, say, your organizations as whole to, perhaps, gather some data like that or are those metrics something that are possible uses for measuring the impact of inspections on overall operations?

MS. GUSTAFSON: I am definitely willing to take the idea back. But I think what you have is the issue of near misses, that if you didn't have a quality program and these things got out, what would be the impact. I know on a company-wide basis, those are taken into account. Whether they have been looked at in the

aggregate by the industry, or whether it would be possible, I am not sure.

MS. JOHNSON: Any other questions or comments?

Hearing none, thank you, Mary.

Our next speaker is Russell Madsen. He is the Senior Vice President, Science and Technology, representing the Parenteral Drug Association.

Parenteral Drug Association

MR. MADSEN: Thank you very much. PDA also appreciates the opportunity to present comments to you today. For those of you who are not familiar with PDA, PDA is an organization of individual members devoted to pharmaceutical science and technology, some research. We have been around since 1946.

Our basic goal is to provide a mechanism for members to get together and share scientific and technical information.

The purpose of this presentation today will be really to cover the four main topic areas, to explain them a little bit and then to provide just some starting points for discussion with respect to ways that they might be addressed.

Those four topic areas we have already talked about are industry compliance with applicable laws and regulations, consistency of inspection and compliance

activities, and the effects of those inspection and compliance activities on product quality, and then, overall, the impact of the Team Biologics Program on public health.

PDA will submit more detailed written comments to the docket by the June 10 deadline. So these are kind of preliminary comments at this point.

In terms of the compliance with applicable laws and regulations, industry wants to comply with laws and regulations, by and large. I don't think there is any question about that. However, companies and regulators sometimes have different interpretations of what the requirements are. This can lead to some problems. In addition to that, some individual inspector interpretations sometimes become a factor in 483 observations.

How can we address some of these situations? First of all, I think it is important to try to analyze and identify what the major areas of noncompliance are and, when they are identified, to develop guidance to try to improve compliance in those areas.

Maybe one way to do that is to develop a system where we can measure repeat findings somehow to determine what the effectiveness of those compliance programs is. Finally, this is an area that was quite substantially

addressed at the recent PQRI FDA meeting in Washington; categorize observations as critical major and minor as they do in the U.K. and then develop a system whereby you could measure compliance by evaluating the number of critical observations per year divided by the number of inspections.

I think this is just one possible way to do this. You have got to be very careful to somehow figure out a way to normalize this maybe with some kind of a five-year running average that will minimize the noise and will prevent you from seeing what is a real change versus what might be a subjective change.

In terms of consistency of inspection and compliance activities, these are some of the issues we identified. Some investigators--this is not the majority, but some investigators seem to focus on building a case rather than looking at what is really happening with a firm and the facts of a particular situation.

In some cases, inspectional outcomes tend to be driven by how individual inspectors interpret the GMPs. Finally, some inspectors at not adequately prepared. We have seen instances where they have clearly not reviewed the BLAS or SBLA and are not aware of particular

agreements between the CBER reviewers and the particular company being inspected.

How can we change this? Well, I think it has been already addressed here. One of the major ways to do this is through investigator training and, perhaps, even certification of investigators for particular areas of competence. Then you could select investigators and match them up with what a firm is doing to make sure that they are fully aware of all of the technology that they need to know about before they do the inspection.

Develop mechanisms for oversight of investigators, effective mechanisms investigators. And then, review the issues that investigators are citing and decide which of these issues should be policy underlying the team-biologics inspections and then communicate those to the inspectors.

Finally, and this was brought out at the GMPs for the Twenty First Century meetings, develop an effective dispute-resolution program.

How can we measure the effects of inspection and compliance activities on product quality? It is very, very difficult. These are some of the issues we identified. The primary goal of FDA inspections and compliance activities is to protect the public health. That is Job 1. Having said that, that is a very broad

issue and very hard to measure. If we do that, if we continue to focus on protecting the public health, over time, this should result in improvements in product quality.

Some metrics that we have already talked about include things like increased customer satisfaction, reduction in nonconforming product and reduced cost, and, finally, the point that this slide makes is that the association between inspection and compliance activities and product quality is extremely difficult to measure and, at best, is very indirect.

How can we address some of these issues? Well, perhaps, if we could develop methodology that could more accurately measure the effects of inspection and compliance activities on product quality, that would be a step in the right direction.

I, again, hesitate to put some of these up here because they have to be handled in a very careful way. But, for example, the number of recalls due to known product defects, and Terry Munson addressed this a little while ago, just because a product is recalled, you have to make sure that there is, in fact, a known product defect involved as opposed to some other issue. Evaluate the number and type of complaints and identify related inspection findings if possible.

The impact of the team-biologics approach on public health; certainly effective products almost invariably have associated potential for harm if they are not used properly, if they are not manufactured properly. Significant adverse effects and contraindications are identified on approved product labeling. Post-approval, serious and unexpected adverse events associated with the use of a therapeutic agent reflect, usually, a previously unidentified risk. However, that serious adverse event may be associated with a product. It could be associated with a user error or some quality defect.

The team-biologics effect can have a negative effect on public health if it inappropriately raises the compliance bar that results in increased product costs and, in some cases, product shortages.

Suggestions for change; if we calculated the reduction of serious or unexpected adverse events, normalized somehow to the amount of product distributed, that could be a measure of the effectiveness of agency inspection programs. Since the agency currently captures both product distribution and serious unexpected adverse-event reports, this metric might be tracked using existing FDA systems.

It is also consistent with the team-biologics goal of an operational and policy approach that fits within FDA's existing structures and systems.

That concludes the presentation. I would be happy to take any questions.

MS. GUSTAFSON: Mary Gustafson, PPTA. You had mentioned the issue of inconsistent application of policy or interpretation. I think that is a common complaint. On one hand, we would say, "Provide us with more detailed guidance," but that is also a double-edged sword because very detailed guidance tends to, I think, inhibit innovation.

Do you have any comments on how this could be improved?

MR. MADSEN: You hit the nail on the head. Guidance has to be general but, at the same time, it has to be specific. We can't have that. We can't have both. Possibly, one way around this is to provide some kind of a template that can be used to identify certain critical areas, critical processing areas, perhaps, that a firm would use to submit, in this case, with, perhaps, a BLA or, in the case of CDER, an NDA or an ANDA.

That would be evaluated by the reviewers, the associated reviewers. Once that was done and agreed upon as adequate, that could be used as the basis for

inspectors to evaluate a particular firm based on those previously agreed parameters.

In addition to using common GMP--so, somehow, it would have to be melded at the inspection level which is not an easy thing to do, but the way, you would get the specifics through this filed and approved application which would be different, perhaps, for every inspected firm and you would also have general guidance out there to cover the GMP interpretation. It is just an idea that has been kind of floating around out there for a while and I don't know whether it would work.

It is a very, very difficult question.

MR. MASIELLO: Steve Masiello. I will ask you sort of the same question that I asked Mary just to be fair. If PDA does any type of trending with members in terms of customer satisfaction and, then, could you comment on how one might define customer satisfaction a little bit?

MR. MADSEN: I will answer your question in two parts. First, PDA really doesn't collect any data on customer satisfaction. What is customer satisfaction is the second part. I think I would define it--other people would define it differently, but I would define customer satisfaction in terms of FDA's inspectional efforts as agreement following an inspection, that that inspection

was fair, it identified the issues, that those issues were correct and agreed to by the firm.

Nobody likes to be inspected, but everybody knows that there should be a system of checks and balances and you have to have inspections. But if a firm is happy with the results of the inspection, assuming it is a good inspection and not just a quick brush-through--if the firm is happy and the FDA is happy, then I think, in my mind, that defines an effective program and it defines customer satisfaction.

MR. MASIELLO: So there is a desire for a more comprehensive inspection?

MR. MADSEN: No; but a good inspection. Let me just put this in perspective. I was involved, for many, many years, in my career as an internal auditor--we did inspections all over the world of company facilities and contract facilities and suppliers that we used.

You get a feel for what is a good inspection and isn't a good inspection. You intuitively know that as it happens. You can tell by the inspected firm's body language, if they are happy. A lot of this is very subjective. It is hard to measure. It is hard to quantitate. But you know if it is a good inspection.

A firm appreciates a good, fair inspection that identifies the issues but that doesn't go too far. What

is too far? Again, who knows? I hope that answers your question.

MS. PRESTON: Sue Preston. I have a couple of practical things, but, before I get into that, can I talk about a philosophical question. You raised an issue here that heightening of the compliance bar may result in increased production costs and, therefore, those are transferred to, obviously, our customers.

I am a little worried about that being actually a way of preventing products coming to the customers who do value having the choice and having that availability. It is a very insidious way, I think, perhaps even more because it is not as visible as the product shortages that the FDA keeps in their website.

So I am wondering if there is a way to look at the impact of compliance on the increases in costs of products even though pharmaceuticals are less than 10 percent of the medical healthcare costs here in the U.S. So I am wondering if it is worth taking a look at that impact in some more formal way.

I don't have the answer about how because I have been struggling with that question for a number of years. But I think that that would be worth it. I was wondering if you had any comments about that before I have two practical things to mention.

MR. MADSEN: I would agree that it would be very nice to try to find a way to measure that. I would agree with you that I have not thought of a good way to measure that. Maybe somebody else has.

MS. PRESTON: Maybe somebody will think of a good way. Maybe we can put some of the post-docs or some of the doctoral students at one of these pharmaceutical sciences universities. Anyway, a couple of thoughts of about effectiveness and how one might measure effectiveness of the compliance program or of auditors.

I think there are a lot of companies that have fairly significant compliance programs and I am wondering whether, as part of a survey, whether industry would be willing to share how they measure their compliance programs, their auditors and what training they do because, obviously, we have the same goals of our compliance programs as the FDA.

We are concerned about product quality. We are concerned about product quality. We are concerned about the public health also. So I am wondering if that might be also helpful in looking at that for team biologics. Then, with a specific thought to the inspections; now the inspections seem to focus on what I will call our "dirty laundry." And, yes; it is a very effective way to tell what we are doing with respect to the product quality.

But I am wondering whether it would be more effective to switch to looking at areas of prevention. So, in other words, do we think about the standards for our facilities. Are there some standards for quality systems that we could use? So I am wondering, instead of focusing on, I'll say, the tail-end, can we look at more of the input end and influence that and have a more effective impact on compliance.

MR. MADSEN: Again, very difficult questions. There are lots of ways to measure the effect, I guess, rather than the effectiveness of your audit program. You can calculate things ranging from how many observations did a particular investigator find in the course of a day or in the course of an inspection. I don't know how meaningful that is. Are they just nit-picky things that Harry didn't cross the "T" when he signed his name on his production record or are they real?

I think one has to look in broader terms at a firm's state of control. That is an old term that goes back into when the GMPs--when I remember, back in the mid-70's, when the GMPs really started to be enforced, some of the old-time FDA inspectors, and I think maybe some of you in this room still remember him, Bud Loftis. Bud always used to look for a state of control, whatever that was.

It is hard to define but I think if you could identify it and feel in your gut that a particular firm had adequate control and production-and-control systems in place that they knew what was going on in their organizations, that you didn't get a lot of blank stares when you went in and asked a question about why do you do this, if you could find a way to measure that, that is what you are looking for.

But I don't know how measure it. I am not sure anybody knows how to measure it.

MR. BRUCKHEIMER: Mike Bruckheimer with Novartis Pharmaceuticals. I just want to touch on one of your slides where you talk about the impact of approach on public health and you discuss the issue of SAEs and, in principle, adverse-drug-event reporting.

The one comment that I would have on that is if there is anything that could be considered within FDA for an alignment of the inspection effort and approach to adverse-drug-event inspections that a company may experience from both team biologics and from CDER. The reason I bring this up is the office that generates most of the inspections in that area come out of CDER through ORA.

Occasionally, you see a specific team-biologics inspection of therapeutic products which are in CBER's

purview. A lot of the system issues at the company were covered by ORA and CDER. If there is any way that this could be coordinated and aligned, I think it would be beneficial for all of us.

MS. ROSSITER: Emily Rossiter, Regulatory Resources. I guess I would like to underscore Sue's earlier comment about trying to focus on the positive aspects or turn the dirty laundry into something useful. The quality people in our organizations want to celebrate the errors. They really do. They want to encourage the reporting of deviations and problems, but it is very difficult to do that when the staff see in the headlines, week after week, how those same reports can potentially be used against their employer.

So the people who were supervising and managing these employees on whom we depend to report problems are hearing two different messages, one from their bosses and one from the public-health authorities. I don't know how to solve that except to try to get their employees and the public-health authorities talking the same way about these problems and trying to solve them together rather than being used in a "we found this out; it goes in a 483," et cetera, et cetera, and ends up in the Nightly News.

MR. MADSEN: Let me say one more quick thing about this idea of critical major and minor observations classification. It is difficult, sometimes, to know which box to put an observation in but I thin, in terms of some metrics to measure the effectiveness of your programs, if you could somehow concentrate on the critical and major issues and don't include the minors, it might take some of the noise out of the system.

Ten minor observations probably indicate that maybe there is a major one there someplace. If a firm has hundreds and hundreds of minor observations, clearly that is an issue. But the metric, whatever it is when it is finally chosen, or the metrics, should try to identify the critical and major issues as opposed to the noise.

MS. LITTLE: Russ, in one of your slides, you mention that investigators were sometimes not adequately prepared, that they did not review the BLA or the BLS-BLA and are not aware of the agreements between CBER reviewers and the company. I just wanted to point out that core team investigators focus on post-approval inspections so they really aren't required to review the BLA. But they are required to interact with the scientists and the product specialists in CBER.

So I was wondering if you have any data on how frequently investigators are not prepared to do a GMP inspection versus focusing or knowing about a BLA.

MR. MADSEN: I don't have hard data. This is really information that comes in occasionally. I don't know whether it is 50 percent. I can't imagine it is, but there is some low level of that. It is not only in CBER. We see it in CDER as well, particularly for pre-approval inspections. It is clear that the investigator, in some cases, has no idea--sometimes, they don't even know what product they are there to look at when they walk in the door.

We have had some, "What am I here to look at today?" Only occasionally, but sometimes, that is the case. Most of them do their jobs very, very well and are well prepared, but there are some that could be better prepared and trained better.

You can say that same thing for industry. There is a bell-shaped curve and you have got to try to fix that.

MS. LITTLE: Thanks.

MR. MADSEN: Terry?

MR. MUNSON: Just a follow up on the critical major-minor. In most cases, the definitions there are the criticals, are where the investigator can justify

that their failure to do whatever they are observing will result in a bad product. In other words, it is a direct link and they are able to make that connection.

The majors are there is a possibility of that. Then you get into the minors which are just kind of the--well, they are deviations from GMPs, but product impact really can't be--there is not a good direct link to it. So I think, again, using that kind of a model with clearly defined definitions for each one of those, I think, again, focuses on looking for those kinds of operations with a company that does have a direct effect on the acceptability of that product for use by the consumers.

So I think, again, it is a way of kind of refocusing us on what is really important and having the investigators have to actually start linking these things to definite product impacts; how does this observation directly impact this product.

If they can't make that linkage, then it drops down in the criticality scale and they can be correctly judged so that you are looking at, if I use this as a metric, we really shouldn't have a whole lot of criticals out there. If we take a segment of the industry, blood collection, blood fractionation, vaccines, if we are seeing a lot of critical observations in one particular

area, then that would be a key for CBER to refocus on that, and what kind of guidance could be put out, specific, nonspecific, goals, risk-based approaches that should be done which kind of fits into the general FDA movement to go to more risk based.

Maybe that is the idea in the guidance document, how would you go about defining those risks; should each company define those risks for all their processes and have that clearly defined up front so that, when you go in to do an inspection, you focus on those critical points in the processes and how well are they controlled.

MR. MADSEN: Mary?

MS. MALARKEY: Mary Malarkey, CBER. I have a comment and then I also have a question to follow up on this critical major-minor issue. First of all, the comment. I just wanted to assure industry that the dispute resolution guidance and pilot program that are being developed under the GMP Initiative will apply to the team-biologics inspections. So we are working on that as we speak.

My understanding of the European program and correct me if I am wrong, is that the critical major-minor designation is not given by the investigator but rather the findings are taken back to the inspectionate,

if you will, and that decision is made by a further review.

Practically speaking, how do you see that working here? If the investigators, themselves, made that distinction, would we will have consistency issues? I am just wondering how you envision going to that type of system here in the United States.

MR. MADSEN: It would, I think, require a change. Some of this was brought up down at the PQRI meeting. The FDA investigators are required to leave the 483 before they leave the facility. One change that would have to be made under the European system is that that 483 somehow would have to be massaged and the criticality determined prior to the end of the inspection.

That has the advantage of providing maybe a needed link between--I don't know who would make the decision, whether it would be made at the district level or whether it would be made at the Headquarters level, but it would tend, in itself--the setting of the criticality could provide a necessary link between the field and Headquarters, perhaps. But the negative side of that is it might extend the investigation. It might require a change in the way FDA does the investigation in terms of, "Okay; I am finished now. I

am going away and I am going to come back in two weeks and hand you the 483," which would require a law change.

MS. JOHNSON: Any other questions? If not, I have just one thing, Russell. A couple of times during your talk, you mentioned reduced product cost. I am just curious as to whether you feel that is something that industry would be willing to share with the FDA if we were to use that as a metric.

MR. MADSEN: I don't know. I know industry is extremely cautious about cost information. It would be nice if it could be shared. Intuitively, you can raise the level of compliance so high that, at the extreme, products are hand-made, make one tablet at a time and you--it is made by an expert and nobody could afford it.

At the other extreme, it is also a problem. But there has got to be some window of adequate compliance that ties in, somehow, to adequate product quality. The trick is finding where that optimum window is.

MS. JOHNSON: Thank you. Are there any others? If not, we are going to pause here for a break. We are a little ahead of schedule. It is twenty minutes to 10:00. If we could reconvene back here at ten minutes after 10:00. That gives you thirty minutes.

[Break.]

MS. JOHNSON: Our next speaker of the morning is Shannon Penberthy, Senior Director of the MARC Association. She will be representing the National Hemophilia Foundation.

National Hemophilia Association

MS. PEMBERTHY: Good morning. Again, my name is Shannon Pemberthy. I work as Senior Director for MARC Associates. We represent the National Hemophilia Foundation and have done so since about 1985.

Thank you for the opportunity to speak today about the importance of the team-biologics program. For those of you in the audience who are not familiar with the National Hemophilia Foundation, it is a fifty-five-year-old organization dedicated to improving the lives of people with bleeding disorders. They are based in New York City.

We have an extensive number of educational programs usually designed around helping new parents with children newly diagnosed with hemophilia, particularly programs focused on teenagers and then with adults, particularly those transitioning into adulthood.

We have ongoing extensive blood-safety surveillance oversight activities the we pursue; educational programs around women with bleeding disorders; a strong advocacy program here in Washington,

D.C. focused on research, education, prevention, treatment for hemophilia and for the complications of hemophilia and also for bleeding disorders.

We have I guess about forty-five chapters now nationwide and we are the largest of the hemophilia, bleeding-disorders, organizations in the United States

I know this was offered a little bit earlier by Mr. Bowers in his presentation but a little bit about the history of team biologics, at least from the NHF's perspective. In some ways, we really feel the origins of the team-biologics concept came out of the handling of the HIV-AIDS crisis. As consumers become more involved in trying to understand how their products that they used were manufactured, how they were inspected, the FDA's role, all these questions asked about what happened in the '80's.

It became clear that something more needed to be done. These concerns gained emphasis and validation with the Institute of Medicine Report on HIV in the blood supply. As you will recall, the report made some very specific recommendations about improvement in our blood safety and blood-supply system.

We were also, at that time, I would say fortunate to have a member of Congress who took a very strong interest. His staff as well took a very strong

interest in these issues, and there were a number of hearings that those of us who were around then--I don't know if we finally recalled them, but there was a series of hearings that occurred actually over a number of years and the government formed an oversight committee.

Those really began in October of 1995 when the Congressmen Chris Shays, who chaired the Human Resources and Intergovernment Relations Subcommittee of Government Reform and Oversight, held a hearing on the IOM Report that then Secretary Shalala testified at. It was really, if you will, the Administration's first response to the IOM report, a number of recommendations put forth then is how we now have--the Assistant Secretary of Health is the Blood Safety Director. There is an internal task force within the Department on blood safety. Then, further, there was the establishment of the Advisory Committee on Blood Safety and Availability.

I recall all that because we also testified, the Foundation did, at that hearing. I actually pulled out the testimony. This was testimony given by a mother of a hepatitis-infected child with hemophilia. At that hearing, we called for FDA to work with manufacturers to expedite the development of new viral-inactivation techniques, for the development and enforcement of a system for notifying providers, potential purchasers and

known consumer groups about potential threats to blood products from infectious disease.

We advocated for smaller plasma pool size. We advocated for consumers of blood products to be vested participants in regulatory commissions and meetings on blood policy including the Blood Products Advisory Committee. We called for accurate warning labels to be developed for blood products and we also called for a compensation fund.

I went back to that testimony because I thought it showed, in a way, how far we have really, really come. That Committee went to have various hearings and had various reports that were referenced, the OIG, the GAO reports. Some of the findings from those hearings actually were that the blood supply is safer than it has ever been before, that it continues to face new infectious-disease challenges, that HHS had begun, at that time, to implement higher regulatory standards for protecting blood and blood products, that the public has insufficient information on the risk of blood and blood products, that management of the regulatory-review process was needed by FDA and that we still did not have an effective communication system.

This was August of '96 when that report was put in place. I guess I would say we have made a lot of

progress in some of those and there are some we still need to work on.

I think that it should be noted that those hearings were occurring at a time when we were having numerous product recalls and shortages of products. Unlike the recalls and withdrawals of the '80's which were caused by the transmission of hepatitis or HIV, these were recalls that were bacterial in nature. We were having products show up reactions in patients because of sepsis or because, in one, penicillin mold had been found in the vials that the product was put in and then it was shipped.

I think that these are the types of things that team biologics and greater enforcement of good-manufacturing practices in those facilities have addressed.

Another key turning point in our minds is a meeting that we had in 1997 with FDA with senior officials. The Foundation had been trying to meet with FDA for some time and finally was granted a meeting. Some of the questions that we raised were the same ones being raised in the hearings; why weren't facilities that manufacturer biologic inspected by people who had an understanding of blood.

On the other hand, why weren't plasma manufacturers held to GMP standards like other drug and device manufacturers? Why, in spite of the problems of the '80's and the IOM report did the phone call about a recall still come to my office every Friday at 5 o'clock and I would be left all weekend with this information?

It got so bad, we would stand by the phone and wait for it to happen. I am really not joking about that. We think that team biologics has addressed these questions for our community by beefing up inspections, holding manufacturers more accountable to GMP and ensuring the efficacy and safety of blood products.

We believe team biologics has been crucial to the improvements we have seen, and I don't say that lightly. Our foundation has been criticized, at times, by manufacturers, by blood bankers and even our own community about some of the shortages that have recurred because of those more vigilant inspections.

Some of the facilities, the production lines had not been inspected in years. I know I recall from one of hearings that one of the albumin lines had not been inspected in forty-five years. So you are going to expect any time that you change practice and start to enforce things that you hadn't enforced before that that is going to have an impact.

I know that availability is a safety issue for our community. I think that, because of the history of the hemophilia community, we tend to fall probably more on the side of--we can work around the availability issue but let's first make sure the product is safe. I think that you saw that in the shortages that occurred just a couple of years ago.

Prior to team biologics, we really were plagued with these recalls and withdrawals. I pulled out old recall data. In 1996, there were fourteen product recalls. Last year, in 2002, there were four. But I agree with the point made earlier; you can't just compare numbers. What was the impact or the severity? What was the critical problem, if you will, with those products that caused the recall or the withdrawal.

In 1996, it was because of transmission of hepatitis. It was the sepsis. It was the penicillin mold. In 2002, those recalls were because there were concerns about the efficacy of the product related to manufacturers today trying to meet consumer demand for a product that is not refrigerated.

What we have found is that some of the products that we thought didn't need to be refrigerated, in fact, when they were kept at room temperature for a certain

period of time, don't have quite the same potency that it is labeled for.

So I very much agree with some of the comments made earlier in terms of where are we in terms of critical transmission or the reduced potency. It is a safety issue but not of quite the magnitude that the product recalls were earlier, just even six and seven years ago.

Transmission of viral contaminants fortunately is very low today, although we must remain vigilant in our efforts of monitoring new agents, West Nile virus, SARS, even CJD remain very much on the minds of consumers of blood products.

Consumers then have brought more into the decision process. We now have a voice on all the federal advisory committees related to blood. NHF has regular meetings and a dialogue with FDA in a collaborative manner that previously did not exist. I think this relationship has been beneficial to all parties.

FDA has also improved its response mechanisms for communicating information about recalls and withdrawals. We now actually have a voluntary notification system maintained by PPTA. We continue to think there could be some improvements to that system but we are certainly a long way from where we were.

So, obviously, much has changed since the now eight years since the IOM Report was put into the place and the three or four or five years since team biologics was instigated by the agency. But I would contend that some of our central issues of safety really have not. I think we are getting closer and more discrete and finite in our questions, can we get to zero tolerance in blood, what new pathogens might be out there that put these products at risk, how much verification and validation is needed to maintain safety, efficacy and consumer confidence in these products.

I think one place to start is to look at the different layers of our blood-safety system starting with donors for these products. What can we do--and I know this is a very hot topic right now, but what can we do to ensure the equivalency between paid and volunteer donors. Is that something that is achievable and, if it is not, why not, and getting those questions out on the table.

Inspections; there was a lot today said about the 483 and consent-decree process. It is something that we have a lot of questions about. We, obviously, will also look at the 483s and, like Mary, would like to see the data behind that so we can have a more full understanding, really more to put the findings in context.

Today there was talk about critical, major, minor. I would never say leave the minors off because we need to know about those and track those just as much as we do the critical and the majors. But what is the context? We currently are engaged in a dialogue with the American Red Cross about the December 483 and the revised consent decree.

But, as consumers, it is almost like a three-legged stool in that we talk both to FDA and American Red Cross and it takes a lot of those conversations and continuing dialogue to help us put in context what this really means and what is the impact.

We appreciate that is a dialogue that is also continuing privately with FDA and American Red Cross but trying to interject ourselves into that has been extremely important to us to have a better understanding. We have to scratch our heads a little bit and say why is it that we are ten years into a consent decree and the problems haven't gone away.

I think that does require a bit of a paradigm shift. There was a comment made earlier today about we focus a lot on what was wrong when we go and do an inspection. Maybe we need to focus more about what was right and try to address in a whole systems manner how

that prevent from getting to the situation where you have a consent decree.

I know when you are starting with a bad situation, it has hard to go there. But I think it is something that we need to discuss as, hopefully, an entire community.

Viral inactivation; our consumers want rigorous testing for new agents as they come about but how much testing can you do? When is the data enough? CJD has been out there for how long now; ten years? We are still just getting to a point where we are considering changing the label for the product.

Sometimes, the science isn't there to be able to make those decisions. We have actually encouraged, or are encouraging right now, the development, if you will, of an emerging-threats matrix that would help, we think, everyone involved be able to, hopefully, get to that decision about whether something is a potential threat in a quicker method.

We now know from our very in-depth conversations and the presentations in monitoring these issues that you can have a new threat that resides within a family of things that you know are inactivated. We have seen all of the test results from the spiking with West Nile virus and bovine diarrhea. Is there a list somewhere that we

could say, "These are the things that we know currently are inactivated and these are the things that we know--" I guess the unknowns, you don't know. But can we extrapolate that somehow.

We have also very much supported the development of new technologies for inactivation and for testing. One of the things that we are aware of is a microassay that would simultaneously speed up and reduce costs for testing. That is something we very much are interested in and have supported.

We were asked, for today, because, as a consumer organization we are not involved in the everyday, when the inspector comes in, the inspection process, but we were asked to propose new ideas for measures. I do think you have to go beyond just measuring. We had fewer recalls, trying to put those recalls, when they do occur, into context.

For us, shortages are an issue. I know we were quite frustrated in the previous shortage in 2001 that we couldn't get the shortage on FDA's official shortage list because that list is maintained by CDER and not CBER. We were, nevertheless, quite pleased with the way that FDA mobilized its resources in speeding up some product approvals and some plant approvals to address that supply issue.

I think one of the things that we think about is that we tend to only, as consumers, and I say that not only as the national organization but also thinking about the mother of a young child who is infusing this product pretty much on an everyday or every-other-day basis--we only hear about the problems. We don't hear about when the inspections go well. We don't hear about when a facility has passed an inspection.

I don't know if that is something we could ever get to or not. Occasionally, you might have a manufacturer who is bold enough to come out with that statement following--if we moved more to that kind of system, or where you let that information also be known, I think it would go a long way towards instilling more confidence in consumers about products and, I think, create some joint accountability between FDA and the manufacturers about being able to make that statement.

I have already addressed that, like many, we sometimes want to see the data before--in the 483. If I go through FOIA, sometimes some of the critical information that we need to know is scratched out and, therefore, we are put in a position where we are really reliant upon conversations that we have had with FDA and the manufacturer to try and help us put all the pieces together.

I think that, by and large, our members and our consumers don't fully understand the inspection process. That is something that also could go a long way towards, I think, improving confidence. If our consumers had, in somewhat laymen's terms, a document that said, "These are all the things that occur in an inspection. These are the things that are evaluated, looked for," in very generic terms, it would help, again, our community put in context what it means when a 483 is put together post-inspection, what are the steps in terms of what gets you to a consent decree.

There was also a comment earlier today about customer satisfaction. In my opinion, and in, I think, most of the people in this room, the ultimate customer is the user of those products. They want a product that they have confidence in, that they are going to have, if you will, consistent results with, that they understand, to the best that can be done today, does not transmit disease and that is readily available when they need it.

The IOM Report begins by stating that blood safety is a shared responsibility. I think, to maintain that safety, we do all have to work together. I actually pulled out of FDA's own website a piece they have on what they believe their responsibility for blood is. The very last sentence is, "The role of FDA is to drive risk to

the lowest level reasonably achievable without unduly decreasing the availability of life-saving resources."

I think that is something we wholeheartedly endorse and believe that team biologics has done a terrific job in further moving us towards that goal.

MS. JOHNSON: Thank you so much.

Any questions or comments at this time?

MS. PEMBERTHY: I had to have sparked something. I apologize for not having a formal presentation. I was asked to do this on Monday afternoon.

MS. JOHNSON: Hearing none, thank you very much.

Our fourth and final presenter this afternoon is going to be Miriam O'Day representing the Immune Deficiency Foundation.

Immune Deficiency Foundation

MS. O'DAY: While the slides get set up, I will just introduce myself. Again, I am Miriam O'Day. I am here with the Immune Deficiency Foundation. I would like to say, on behalf of their Medical Director, Jonathan Goldsmith, who was supposed to be presenting today, he is very sorry that he could not be here. I would also like to acknowledge and thank Candice Steele, the Vice President of Communications for IDF. When you see the slide set, you will realize how good she is going to make me look today.

When we took a look at the Federal Register notice, we decided that what we really wanted to address here today at this meeting, and we are pleased to be able to have comment on the record, are Questions 3 and 4, the effects of the inspection and compliance activities on product quality and the impact of this approach on public health.

The Foundation's mission is listed there for you. To boil that down, it is really to improve the quality of lives for individuals living with primary immunodeficiency.

I am going to give you a little bit of background on IDF, use a case study on the Bayer tampering recall and talk about some of IDF's actions in that regard, and then make some recommendations in terms of improving community outreach, collaboration and, we hope, through that collaboration, improving public health.

The Foundation was founded in 1980. The individuals who founded it were parents of a child that was diagnosed with hypogammaglobulinemia. He was two years old. He was in the hospital for his third pneumonia. They decided that what they really wanted to do was to form an organization that was national in scope. There were some support groups around the country

but people, because of the rarity of this disorder, and rare diseases are defined as 200,000 or less in the U.S.--because of the rarity of this disorder, there was not a lot of lay public information available and people had not met one another who were affected with these disorders. It was very difficult to find other families that had children with X-linked SCID or hypogammaglobulinemia.

The organization has a Board of Trustees. The Board is comprised of individuals, again, who are primarily personally affected. It has a medical advisory committee with twenty members and all of them, I should note, are leaders in the field of immunology. In fact, some of the members of the MAC are the ones who wrote the textbooks on immunology, some of the basic texts on primary immunodeficiencies and immunology.

A nursing advisory committee was formed by the Foundation in 1999. They have a volunteer peer-support network. They decided that the chapter structure was not as effective as having peer support all around the country, so they have a large volunteer network now that can be mobilized on issues and a professional staff.

They are accountable, personally affected and invested in the success of the organization. Because of all of these advisory groups and committees and the

activity of the Foundation, their reach is extensive. The patient and family members around the country, the majority of them have probably heard of the IDF if they are not engaged on the mailing list and having regular interaction.

Healthcare providers are regularly updated through participation at professional society meetings, presentations to national pharmacist meetings, et cetera. They have a legislative federal and regulatory outreach program and we will talk about that a little bit more in the milestones.

All of the healthcare community has had some type of outreach by the organization. They partner closely with industry. They have an interactive website and conferences and regional meetings around the country.

In 1980, again, the organization was founded. The Medical Advisory Committee was put together. In 1987, they published their first patient handbook in primary immunodeficiency diseases. Again, please feel free to contact the organization if you would like a copy of the handbook, it is very impressive. It covers all aspects of primary immunodeficiencies including nutrition, healthcare, all types of healthcare, et cetera.

The Foundation helped form IPOPI, the international patient organization for primary immunodeficiencies, to help address international issues. As you know, healthcare is much different in Europe and other parts of the world than it is here. The challenges of organizing patient groups are extensive, so the U.S. offered leadership.

In 1994, the organization really realized one of its primary goals which was to establish a patient registry. NIAID, the National Institute of Allergy and Infectious Disease, awarded a grant for the Chronic Granulomatous Disease Registry, the first of its kind in the country, which is significant because it led to an additional award in 1997 of eight patient registries which includes common variable immunodeficiency. CVID makes up the majority of the diagnosed population. So the Immune Deficiency Foundation now is tracking CVID patients.

I want to go back and just note for you that the registries are physician registries. The physicians register patients and they are medically qualified. There is PI. This is not patient-reported data that is in the NIAID registries.

In 1998, as a result of severe shortages, as a result of problems in manufacturing GMP, et cetera, IDF

established a Safety Net Program. This was a way to do direct-to-patient allocation of IGIV, when the impact of the shortages was severe, across the healthcare system, all sites of delivery, physicians' offices, hospitals, home healthcare. The FDA monitored that program and endorsed that program with us, so they assisted us. We also developed a protocol for prioritization.

In 2001, IDF was fortunate enough to have its first Medical Director, Jonathan Goldsmith. He is an M.D., and that is important when we get a little further down the line because having a doctor on staff allows us to do some things that lay people cannot do alone.

In 2002, CDC had the small-pox vaccine issue to deal with. IDF engaged in a debate on that issue because it is a live vaccine and it affects primary immune-deficient people and immune-compromised individuals. The information that the Foundation put out and our collaboration with CDC is available on the website for anybody who would like to take a look at it.

I would also like to note, since we are all at the end of the time line on this slide, that the Foundation has been instrumental in impacting public health in a number of areas. I want to highlight for you the polio-vaccine issue. The Foundation was there with the parents group, the VAP Parents Group, calling for a

change in the polio-vaccine protocol. Not having had live polio in the Northern Hemisphere since 1979, I believe, there was no reason to be giving the live virus out and the people who contracted polio were those who were immune-compromised and, in most cases, primary immune-deficient patients.

The Foundation has also worked to develop a National Health Surveillance Project and is a regular liaison with clinical centers around the country. The National Health Surveillance Project is important because this is the largest plasma user community in the country, regular, frequent and life-long recipients.

Some of the Foundation's programs include a patient advocate. They have a board-certified genetic counselor who does actual case work for patients. The box on the right gives you a breakdown of what patients are calling about, what they are interested in, what they want to know.

You can see that 40 percent of those calls come from new patients or family members who have just received a diagnosis. They, again, provide counseling and education, tools to help patients manage their healthcare, like physician checklists. You can only imagine what it is like to be a parent of a child who has been hospitalized repeatedly for infections and not even

remembering half of what is being said to you when you are standing in the physician's office or talking to the nurse about what is going on. So we provide checklists for them.

The IGIV Safety Net Program, I gave you a small preview of that. That was launched in '99 as an emergency supply. All brands of IGIV participated in providing a priority program for distribution to immune-deficient patients. The program is still maintained to ensure that an emergency inventory is held in the event of shortages again. The margin--we are not going to talk about the marketplace for IGIV today, but the market is very close. The margin between what is produced and what is distributed is a very close margin and any little blip in GMP manufacturing, et cetera, causes a significant program in terms of supply.

I think Shannon touched on that a little bit when she told you about some of the issues that the bleeding disorders are faced with clotting factor. It was developed again with the endorsement of the FDA and the collaboration and cooperation of all of the IGIV manufacturers.

In March of 2002, the Foundation started a Compassionate Care Program. They do not advertise this program. They receive an average of one call per week

even though the program is not--they don't solicit or make it known that this program is available. It is basically word of mouth.

The applicants are reviewed based on their medical necessity and their financial need and then they are given a limited supply or a time-bound supply of IGIV, again based on the evaluation of their necessity.

The Foundation holds national education conferences for patients. They will be having their second one in 2003. They do full education training. They do breakout sessions by disease and support-group meetings, and a Capitol Hill Day where they are able to visit with members of Congress and advance their legislative agenda.

I want to give you a little demographics about the patient population and the utilization. The patient population, the point we hope to make with this slide, is that the patient population is younger than the general population in the U.S. In fact, the Medicare utilization is about 11 percent for immune-deficient patients whereas it is about 14 percent for the general population.

Again, you have this large chunk of individuals who are between 30 and 44. The significant thing about this is these individuals are in the prime of life for this sector here and a portion of this sector, they are

in childbearing years. They are productive. They are working. They are using computers. They are a very savvy population.

In fact, they are an educated population as well, as this slide will show you. Most have had some college or a college degree or graduate degrees. This data comes from a national survey of immune-deficient patients conducted by the Immune Deficiency Foundation. It currently is not published. It will be published within the next couple of weeks.

Again, you find about 67 percent of this population are IGIV users. When I tell you that they are IGIV users, they are frequent and lifelong recipients. They generally receive their infusions every fourteen to twenty-one days. It is a replacement therapy and it is necessary for life. They have, in most cases, no therapeutic option. As other patient groups who are now plasma consumers migrate to other types of therapies, other routes of administration, other sources of therapy, for instance recombinant clotting factor or for individuals with alpha-1 antitrypsin deficiency, recombinant therapy is around the corner.

IGIV users are in the blood supply. They are stuck there. There really is not going to be a

therapeutic option for many, many years to come, or so our Medical Advisory Committee tells us.

How concerned are they about safety? I would say that between the major concern and moderate concern, the majority of the population is very concerned about safety issues.

When it comes to safety and efficacy--this is a very self-promoting slide--their primary source of information, once you get past the physician halo effect, is the consumer advocacy organization, like the Immune Deficiency Foundation.

The Foundation participates on FDA advisory committees. Again, as Shannon mentioned, we have or did have representation on all the committees that have oversight over blood. Jonathan Goldsmith and Charlotte Cunningham-Rundles sit on the FDA BPAC. Jerry Winkelstein, whose term just expired, was on the Department of Health and Human Services Advisory Committee on Blood Safety and Availability.

I would like to note here there was some discussion with the new administration about reauthorizing the DHHS advisory committee. As Shannon reminded you, this is an important place, one of the only places, that consumers can come and discuss cost an reimbursement issues. It is also important because it is

one of the only places where the federal government and all the agencies with oversight over blood come together and discuss comprehensively blood safety and availability in a public forum where there is sunshine and public comment.

I am going to give you a case study of IDF's activities in response to a recall of Gamimune N, 10 Percent, which is manufactured by Bayer. The Foundation has an advisory committee that assessed the risks, informed the community, conducted surveillance and ultimately ended up advocating to improve the product packaging.

The recall was posted on February 1 of 2002. This recall, in and of itself, did not set off an alarm bell. It actually was the second recall that took place in March of 2002 where the customer reported white precipitate in a solution and low protein concentration, elevated chloride and the presence of bacteria.

An alarm bell went off within the Immune Deficiency Foundation, some pharmacists who notified us and the physician and healthcare community as well as consumers. The Foundation immediately convened its advisory committee, its Blood Safety and Availability Advisory Committee which is a subgroup of the Medical Advisory Committee, includes individuals from the nursing

group and also outside consumers. Other plasma consumers participate in that committee.

We initiated conversations with FDA, CBER, and we established as much open communication as we possibly could with the agency. They had some limitations and restrictions. There is no criticism of FDA here today, but it does illustrate one of the problems that arose through this whole recall situation.

We, again, talked to Bayer Corporation, the manufacturer of Gamimune N. Immediately, the Foundation put out an urgent notice and the product-integrity information sheet. Those are pictures of normal and tamped vials. Those were produced by Bayer. Bayer provided those to the Foundation on a slick-sheet and they went out with our mailing. The mailing went to 15,000 patients and professionals that were on the mailing list. A blast-fax was done to physicians and pharmacists who were enrolled in the Safety Net Program and information was posted immediately on the IDF website.

The messages included in that correspondence were "Check your lot numbers. Don't infuse if you have a recalled lot. Examine all vials of Gamimune N and don't infuse if there is visible precipitate. Examine all bottles for evidence of damage." Again, we understood

that this was a tampering incident and so we asked that consumers be vigilant over all product that was received.

The secondary message was that people were encouraged to enroll in the Patient Notification System. There is no surprise here that, when consumers got back to their pharmacists or their physicians or their healthcare providers that they found that the lot numbers were not recorded. We have asked repeatedly--it has been part of the Foundation's Public Policy Program that there be a way to record those lot numbers easily, whether it is peel-and-stick, bar-coding, scanning, whatever it is, that there be a way for those lot numbers to be recorded.

Again, we found in a large number of cases, the patients could not track their lot numbers back. We asked that they contact us or Bayer Corporation if they had additional questions immediately.

There was also distribution of an educational brochure that was produced some years ago when the patient notification system was first put together. It is an education piece that talks about how to keep an infusion log, where the lot numbers physically are on the vial because a lot of times patients confuse the numbers that are on the vial with information on the packaging and, a lot of times, they never see the lot number.

The product comes premixed to them hanging in a bag and they are just ready to be plugged in for their infusion. So they may never actually handle or see the product, itself.

We fielded numerous calls from consumers and the healthcare community. The importance of having Jonathan Goldsmith as an M.D. on staff as the Medical Director is significant because he was able to do an investigation, file an adverse-event report and submit those case reports to MedWatch.

Finally, one of the things we did was advocate for new packaging, tamper-resistant packaging. In fact, Bayer has modified their packaging so we have some really good news here today. The tamper-resistant packaging, in fact, is being checked on a regular basis. We know because we had a recall because the vials went out without the tamper-resistant packaging. So we know that it is being implemented as well, which we feel good about.

Again, we are not knocking the FDA because there was a criminal investigation in this particular case study. But what happened was we couldn't find out the geographic location where this individual had tampered with the product. If we were able to understand that information, we could have targeted and tailored our

message a little bit better in terms of delivering it to the patient community and the healthcare community.

It really was very frustrating. But, again, we would thank the agency for continuing to keep the dialogue open even though we know that they were very limited by some of the things that they could tell us.

So what we found out here is that collaboration works between the federal government, between industry, between consumers, and that we really need to have a further coordination of disseminating patient information back to them.

So we would like to make some recommendations today. We would like to recommend that we continue to communicate and partner with CBER and the medical community about issues that are relevant to IGIV and patient safety. And we have some specific recommendations about how we would like to suggest that that get done.

We would also like to make the record, as Shannon mentioned, that individuals who are frequent and life-long plasma consumers be given an education piece, a lay explanation of team biologics, of terminology, of descriptions of a 483. This can help allay consumer fears because, when you have a child that is being infused with a product, they are dependent on that

product, you don't have a therapeutic option and you hear that there has been a recall or that a plant has been shut down for compliance problems, it is very difficult to understand exactly what is going on. So we think it would be very beneficial to have a lay publication or possibly a lay section on the FDA website.

We would like to maintain our seats on the federal advisory committees that have oversight over blood. We are very pleased that we continue to have seats on BPAC. Currently, the Immune Deficiency Foundation does not have a DHHS advisory committee seat. We would like to turn our impromptu meetings with the agency, as NHF does, into a standing meeting, a regular meeting where we can exchange information and collaborate. We would like to be able to continue to give you updates on the Safety Net Program.

Finally, we know meetings like this today are an example of the federal mandate to do community outreach to get input and discussion and comments and sunshine. We would like to propose a demonstration project to you where the goal would be to communicate current agency activity relevant to the IGIV consumer community and to collaborate in a framework that is well developed.

We could provide a list of ongoing inspections. We could demo the lay literature and materials. We could

publish information. There could even be a guest spot from the FDA in IDF's Advocate Magazine, which is their newsletter. Information could be posted on the website or there could be plans to link back and forth to the website and we would be able to coordinate this with CBER, and we would have a communications plan already well set and evaluated in place if there were shortages, recalls and special notifications.

The outcome of a demonstration project would be to really build a stakeholder's communication model with the agency that could be used with other stakeholder groups. If you developed it through a demonstration project, a program, it could be easily translated into other consumer groups.

So I think we have stated the benefits. The organization is a national organization. Our mission is really to educate and help patients and healthcare providers--again, we have broad national reach--and direct an ongoing access to the patients. In fact, they rely on us. After their doctors, we are the number-two source of information for them.

I know this feels like a car-rental commercial to say we are number two. But, for a consumer-advocacy organization behind the physician, I think that is significant. Again, we have a proven track record.

I would be happy to answer any questions that you may have. Thank you.

MS. JOHNSON: Are there any questions?

MR. McINTYRE: Good morning. I am Scott McIntyre with the Office of Regulatory Affairs. This is a question to Miriam and Shannon to help address your concern about the information that is available or possibly a question that I have is, is it not available. Are you aware that there are currently on the website of FDA and in ORA, an Investigations Operations Manual, the Regulatory Procedures Manual and the Compliance Programs.

MS. O'DAY: I think that it is not accessible enough to individual patients. That is why we are offering to assist in tailoring that information so it reaches its targeted audience.

MR. McINTYRE: They are available on the Internet, public domain. I think, then, what I am hearing is more transparency and visibility. That is in the Commissioner's Initiative to make FDA more visible. So I will take that back to the people I work with and see if there is a way that we can maybe help in that area.

MS. O'DAY: Thank you. I don't know if Shannon had anything. Do you want to come up to the podium, Shannon?

MS. PENBERTHY: I think that, yes, agreeing with Miriam's answer, those documents are not only difficult for our lay community to find. If they did find them, I don't think they would understand them. Even that is something that--we also have a Medical and Scientific Advisory Committee. If they read them, they understand them, but I am not able to fully articulate all the things that are in there to a consumer who is using the product.

I would love to see us have an hour-and-a-half session at one of our annual meetings where we laid that out for consumers in terms that they could understand.

MR. LEWIS: I agree with those comments. Scott has offered ORA and if I could offer CBER as well to participate in the process to put together a handbook for patients that defines the Inspection Program. I think that CBER does participate in your national meetings.

MS. PENBERTHY: Yes; you do.

MR. LEWIS: And we would offer to send representatives for some of those discussions at the meetings.

MS. PENBERTHY: We appreciate that. Thank you.

MS. JOHNSON: Any other questions or comments? Thank you, Miriam.

At this point, we are open for any general questions, whether it be from any of the presentations that were made or any other burning issues you had on your mind that you just had to get off your chest. If there is anyone who wants to make an additional comment, now is the time.

Okay; I think we are all talked out, then.

We are just going to go over a brief recap of the goals of the meeting today. We are going to use a couple of the slides that you saw before from Mr. Bowers' talk. The criteria that we hope to address today were: to develop tools and metrics to assist us in measuring industry compliance with the applicable laws and regulations; assess the consistency of our inspections and our compliance activities; and also to determine the effects of our inspection and compliance activities on product quality and the impact of our approach on public health.

Hearing no additional comments, I would invite you, that if you have anything that you think of later on, we do have a docket that is open. You can write to us at the Dockets Management Branch here at FDA or you may choose to submit those electronically on our website at fda.gov. If you need any more information on exactly how to do that, see Melanie.

I guess, at this point, I will introduce Richard Lewis. He is the Director of the Office of Blood Research and Review in FDA's Center for Biologics Evaluation and Research and he is going to give us closing remarks after which we will be adjourned for the day.

Closing Remarks

MR. LEWIS: Thank you, Anne. I will let Jay know later on. I am the Deputy Director of the Office of Blood. Dr. Jay Epstein is the Director.

MS. JOHNSON: I promoted you.

MR. LEWIS: Thank you very much. I appreciate that.

I think today has been a very worthwhile meeting. One thing that struck me just now in your talk, Miriam, the government requirement to receive information from the public was really not one of our foremost moving concepts in developing this meeting today. In fact, we were stuck. We did come to the question of how can we evaluate ourselves and what are the appropriate metrics to put into place to go forward with team biologics to evaluate ourselves and wanted some public information from that.

We know that manufacturers assess themselves through quality programs and we are hoping to, and think

that we have, received some important information today on how to put some of those things in place.

Let me start by thanking, again, Lee Bowers. He thanked the workgroup that was listed in his slides, some of the people that have been addressing this question. I also want to thank our Office of Communication, Training and Manufacturers Assistance who were very important in putting this together, Melanie Whelan, who is very important in putting together the meeting, as well as Kathy Eberhart and Donna Lipscomb whom you have all seen this morning helping with the organization.

I think that there has been a recognition today that regulatory actions are all necessary and that we keep track of them and that they are one metric that can be used but that are not necessarily a measure of product quality. Again, this is one of the areas where we were hung up, to continue to use these particular measures doesn't really address the quality of the product; that is, our bottom line is that the products get better and that patients get improved therapies.

We want to integrate and implement GMPs for the Twenty First Century--this is also going to be part of our efforts in the future--as well as implementing a more effective inspection program.

We have seen today and heard a greater cooperation with industry and patient-advocacy groups. That is an extremely important component of team biologics and we hope to continue that and like to make that offer, anything that we can do. We do hold regular liaison meetings with both industry organizations as well as patient-advocacy groups and we will hear your comments at those and at other times. I think that even in some of the presentations this morning, there has been a recognition that it is very difficult to establish specific metrics. Where are the boxes that we can put a check in to say that we are getting better or worse? But there is an important subjective component not only of the inspection process, itself, but in evaluating the inspection process.

Some important comments on categorizing 483s, we recognize that there is some difficulty in doing that but that might be an important component that we can address. We regularly, again, collect feedback from industry and patients and hope to continue to be able to do that.

I would like to thank the National Hemophilia Foundation for their comments that team biologics is critical to improve safety and we agree. We think that we do serve an important role and would like to see

ourselves in that role and that is our ultimate goal, is to serve the patient.

So, as we continue our dialogue, I will remind you one more time to please send your comments to the dockets. All those comments are taken seriously as well as the ones we have heard today. And thank you all for taking the time to put together presentations for us as well as those of you who have come to contribute to the discussion.

Thanks a lot.

[Whereupon, at 11:10 a.m., the meeting was adjourned.]

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