FDAMA STAKEHOLDER MEETING

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April 28, 1999

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April 28, 1999 P R O C E E D I N G S 9:34 a.m.

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MS. ZIOBRO: Good morning, everyone.

I think we're going to have quite a bunch more people joining us as we get into this morning's program.

I'd like to introduce myself. My name is Pat Ziobro, and I'm the district director of the San Francisco District in Alameda. And we're really pleased this morning to be able to cohost one of the live sessions with Kathy Zoon from CBER. I'd like to tell you a little bit about the game plan this morning. Our satellite downlink will begin promptly at 10 o'clock with Dr. Jane Henney, our new commissioner, discussing her vision and priorities and the accomplishments we've made in support of FDAMA. Following Dr. Henney, we'll hear some remarks from Linda Suydam, who is also in the office of the commissioner, who will give us additional remarks about where the agency is headed, obstacles we have. And we will be seeking questions, input and so forth during the teleconference as well.

There will be an opportunity to fax and phone in your questions, and I'd like to ask if you have any of those, that you put them on this gray-colored sheet that's in your packet and step outside. Immediately

outside the door here we have a fax and phone line that we can send those questions in directly.

This will be an interactive session, and it's going on all around the country. In addition to this facility here, we have another CBER group on the East Coast in Boston; we have a device group down in San Diego; veterinary medicine in Kansas City; a foods group in Washington; and an ORA group in Washington as well; CBER in Philadelphia. So we have other live sessions in addition to groups that are just hosting the video satellite this morning.

Because we have sessions going on all over the country, you understand that it is possible your question may not be answered live while we're on this morning. But I assure you all those questions are going to be kept and answered someplace in those minutes that will issue. The report will probably be on the Internet. Kathy?

DR. ZOON: Yes.

MS. ZIOBRO: As they have in the past, we have a reporter here who is going to record all the comments and all the live testimony that we're going to have today during the teleconference as well as in this afternoon's session.

At the end of the day, I would appreciate if

you would take the blue sheet of paper in your packet and give us some feedback as to what your thoughts were about today's session. Today is unique in that we are having this all over the country rather than the separate sessions that we held last summer for each of our stakeholder groups.

The video conference will go until about noon. We'll take a short break and resume after that break with our session here with Kathy and your particular interests in the CBER program areas. And then I think we'll take a lunch break and come back between 2:00 and 3:00. Is that correct?

MR. STRICKLAND: Yes. We will have a panel from 12 to 1 o'clock, and then from 1 clock to 2 o'clock will be lunch, and we'll come back at 2 o'clock and adjourn between 3:00 and 3:30.

MS. ZIOBRO: Okay. I'm sure you've all found the rest rooms around the corner as well.

Help yourself, get up during the video conference, to some refreshments in the back of the room.

And again, this is our opportunity to listen to your concerns. We don't have a whole lot to say. We want to listen. Again, I extend a welcome to all of you, and I know this is going to be an exciting day.

It's new for us as well.

DR. ZOON: Thank you, Pat.

First I'd like to welcome everyone. This is a wonderful opportunity to come out to the West Coast to meet with many of our colleagues and to hear how we're doing and what you think we could be doing better, and constructive advice is always welcome, and also to talk with you a little bit about our priorities.

But before going onto that, I want to personally thank Pat Ziobro, the district director, and her staff, Kathryn Macropol, Mary Ellen Taylor, and also Mark Roh for helping us put this on out in San Francisco, and Dennis Strickland, who is here, again, is my deputy director of Office of Communications and Manufacturing Assistance.

Also here from CBER, Dr. Jerry Donlon, who is deputy director of the Office of Compliance and Biologics Quality, and Dr. Lillian Yen, who is the special advisor on medical devices for biologics, are here. And they will be taking over for me at 1 o'clock because I have to go back for a hearing tomorrow morning. So I need to leave at 1:00 to make my plane to get back for that.

But I really appreciate your coming, and Jerry and Lillian will be here subsequently to listen

and answer any questions you have. So thank you.

I would like to give you a brief overview if I can now using some overheads, and I'll speak until 10:00. Wherever I am, I will stop. So just to warn you if it sounds like I'm stopping in the middle of something, I probably will be.

Part of the outreach that we would like to -- you can leave the lights on.

MR. STRICKLAND: Okay.

DR. ZOON: That's not necessary to shut them off.

I would like to just remind everyone about CBER's mission. And that is the mission of CBER is to protect and enhance the public health through the regulation of biological products and related products including blood vaccines, biological therapeutics -- and I have changed the mission statement. We might have it approved by our organization as a whole to include devices based on comments we had gotten at our last 406B meeting.

According to the statutory authorities, the regulation of these products is founded on science and law to insure purity, potency, efficacy and safety and availability.

I think what we regulate at CBER is no

stranger to many of you in the audience. We have a spectrum of products here including blood, blood derivatives, tissues, devices, diagnostics, xenotransplantation and many biotech products.

The regulation of these products is based on what we call our biologic Olympic rings, and it's review, research, surveillance, policy and compliance.

CBER has prepared a vision statement, and this is very much -- is very consistent with what Dr. Henney will be talking to us today about with respect to focusing on the science base. And that is that CBER advances the public health and merits the public trust through high quality science-based regulation to insure that safe and effective products reach the public as rapidly as possible. CBER demonstrates international leadership in regulation through development of innovative regulatory strategies and standards, a managed regulatory process, coordinated research and the use of partnerships. And partnerships can be with academia, other government agencies, as well as the industry. And many of these partnerships have already been established, and we would like to continue.

I'd like to just share briefly our priorities for FY99 as they stand and we have been implementing. One is to implement the FDA Modernization Act, and we've

been working very diligently on that, and you will hear more regarding that from Dr. Henney.

One of the major initiatives that CBER led this year was the fast track program, which is a program for products for severe and life-threatening illnesses. And a guidance document was issued last November which gives comprehensive instructions on that program. And I would refer you to that if you are interested.

The next priority was to meet and exceed our PDUFA goals for FY99. And I'm happy to report to you CBER has met all its goals thus far for both FY98, and we are meeting all our milestones for FY99. So I think we're very proud of that and hope that not only the numbers but the spirit of FDA reform is being exhibited in our performance, and we are trying to pay very close attention that we are doing that.

Take whatever actions are necessary to assure the safety and the public confidence in the nation's blood supply.

A major activity for CBER that was started in the summer of '97 was our blood action plan. This particular plan covers a variety of issues from reinventing our processes, to improving our performance, to getting regulations out. And we have been very successful in this program and have a number of other

milestones that we will be meeting for this upcoming year.

To facilitate the development and approval of significant vaccine, blood and therapeutic products through review, policy formulation, regulation development, et cetera, and to pursue excellence in research that's directly targeted to our regulatory mission.

These I believe are fundamentally important. They are in the spirit of FDAMA. I think that we really are looking at trying to see innovative ways not only to reduce the review time for applications for marketing but also looking at the total development time it takes from when an IND is submitted to when the product is actually approved, because that's really where the rubber meets the road.

Some of our other priorities are to focus on our information systems, and this includes not only within the center but for our review. We have this as one of our prescription drug producers goals. It's part of that program. We have engaged in working on guidance documents that provide support for the industry and others who use these information systems to give you the standards and how we are going to proceed. We've also spent a great deal of time developing our infrastructure

at the center improving the capabilities of our equipment so that we will be in a position to receive electronic submissions, both for INDs and BLAs by the year 2000 and continue our effort to have a high quality diverse work force.

Well, some of our challenges at CBER are shown in this slide. Our operating budget, while it looks reasonably steady, has had some major challenges especially in the products that are non-PDUFA. That's the purple. And we have had a 40 percent decline in our operating budget over the past five years. And this has taken a fairly heavy toll on some of our non-PDUFA programs.

This year we were able to use some of the PDUFA reserve one time to promote and actually give a jump start to the PDUFA II program to insure we could meet the milestones. But I think this will not occur next year, and we need to really be careful to maintain a certain balance on our programs, and I think right now our biggest concern is in the non-PDUFA supported area.

If we look at our workload, the workload at CBER has been, if not steady, but a slight increase especially in our investigational new drug applications, IDEs and master files. This year we had 538 new INDs, IDEs and master files submitted. 60 percent of this

were in biotech products. So I think that's an interesting number. So that two-thirds of what CBER does actually in the investigational area is related to biotech.

The number of licenses we had last year has been -- applications received has gone up slightly although the numbers for the biotech applications are about the same. So for FY 98 we had 77 applications received.

Just to show you our performance with respect to PDUFA, this gives you full cohort years that we have complete data on. 98 and 99 are still in progress. But as you can see, CBER has met or exceeded all our performance goals.

In looking at the future and where are we going, one of the key areas for us to focus on, I believe, to meet the challenges of the new biomedical products coming out into the public as a result of large investments in biomedical research really require an enhancement across FDA, including CBER, of the science base. And this is particularly important to facilitate sound, timely regulatory decisions.

I think when you don't have the proper scientific underpinning, one tends to be more conservative and more timid in your decision making

because you're afraid of making an error. And I think the opportunity to enhance the science, make good scientific judgments, is absolutely necessary for many of us to realize the fruits of the products of new technology.

So what are some of the things that we want to do for our science base?

One is to really focus this on bringing the new products and improvements to products to the market as rapidly as possible while assuring their safety and efficacy. And second is to make sure that we reduce the risks of the products that are on the market while enabling access. Some of the strategies we're looking at to do that include enhancing research, standards development, surveillance, outreach and premarket review.

Many people ask, "Well, does FDA really do research? And why do they do research?" Well, there are some fundamental reasons. One is to facilitate the approval of safe and effective products. Two is to support decisions to withdraw products that are found to be unsafe. And to anticipate public health needs and really provide the support for that decision making and prevention of a public health crisis. It also encourages the adoption of standards and also

contributes to the development of new products. And probably not insignificantly, it aids in the recruitment and retention of scientists at the agency.

Some of the major initiatives that we're currently engaged in at CBER include, as I said, the implementation of FDAMA. We have a strategic plan that we're in the process of implementing. Team Biologics, of which you heard, that we have an active team with CBER and ORA and field in doing a team approach with product and GMP experts and cross-training. And I think that's proceeding quite well. We're almost finished rolling it out. Coming this October, vaccines and other products will be transitioned into Team Biologics, and most of the other products have already been transitioned.

We have a tissue action plan, which I won't have time to talk about today, but that's proceeding well.

A blood action plan, which I had alluded to previously.

And a xenotransplantation action plan to deal with this new technology for potentially using animals as a source of organs and tissues but mindful of the infectious disease risk.

And one of the big areas I'd just like to

mention this morning is device action plan. Last year at the 406B meeting, we had heard your concerns with respect to CBER and its performance regarding the device review and management. We heard you. We put together a device action plan. I'm proud to announce today as of two days ago it has been signed off by myself, Liz Jacobson, Dennis Baker, the new head of -- the new ACRA, Associate Commissioner of Regulatory Affairs, and Dr. Henney. That action plan is now up on the Web. And Dr. Lillian Yen, who is here today, and Dr. Donlon will be happy if this afternoon you have additional questions regarding this plan to be available and discuss it with you.

Some of the concerns we had heard that we were trying to respond to were the consistency with CDRH, harmonization on some of the standards both with the review and the oversight -- compliance oversight and inspections, facilitation of reviews, guidance and communications.

In the interest of time, because we only have a couple of minutes before Dr. Henney comes on, I would just like to say that this particular plan really focuses on four areas: The CBER-CDRH coordination; review performance; compliance including Team Biologics, and having uniform standards; and outreach and inreach

both to the outside communities we serve as well as within our own organization to get the very best ideas to work on needs of particular issues.

The coordination with CDRH includes adoption of certain guidances that CDRH has already submitted, in which one applied to CBER that should publish shortly we're going to be reviewing the innercenter agreement and working on that. And we're also working very hard on a number of areas in terms of re-engineering our processes as well as having joint training with CDRH and having a web page devoted to the CBER devices. We are also actively engaged in guidance documents as they may be unique to the (unintelligible).

In closing, I wanted to just say that we very much value the information and the feedback that we get from these 406B meetings. It's very important for us to hear from you. This is your opportunity particularly today to talk about your experiences, your issues, your concerns and also to give your ideas on how we can do our jobs better, which we will take under serious advisement and discussion.

And I think the device action plan is our response to the commitments that we have to seeing that when legitimate issues are brought to us with ideas, we try to incorporate your ideas into what we have

developed to be responsive.

So thank you very much. I appreciate the opportunity to be here.

(Clapping)

DR. ZOON: Now I hope they start on time.

Are there any questions?

I'm sure I can answer everything, no. Yes?

MS. MAURER: My name is Kerry Maurer of Gene Labs Technologies. My question refers to the fast track program, which I think first off I commend the agency for adopting this type of program, and I use the guideline many times, and I think it's comprehensive. However, I think it's assumed that if the drug is granted fast track that -- or during scientific development or prior to NDA filing that the standard NDA supported studies, (unintelligible) can somehow be waive or postponed into a post-NDA commitment (unintelligible). Is the agency using that vehicle? Activity? Is that something that's really happening, or is that sort of a feeling you get when you get a fast track for your --

DR. ZOON: I'd have to know the specifics. I think depending on the plan you have and how you come into the agency and how you discuss what you think your development plan is, that's something to put on the

table when you come in to develop that.

I encourage many folks when we deal with them that if they actually have a five-year plan that they're discussing with one or more of their products that they actually come in and talk to us about it. One, it helps us to understand what your issues are and what flexibilities you actually have with the particular product, because some of these are very product-specific, and you have to deal with them. In addition, it helps us to understand that there are going to be areas as you go forward and not only for fast track but in your whole development profile what we may need to be looking at down the road because sometimes if standards have not been developed or biomarkers are in the process of being developed, sometimes we can give you advice on that area. Or if there's a big need that we're seeing in certain areas for the development of biomarkers or discussions on others, that puts it on our radar screen so that we can then work with NIH or other interested parties in making that a more public meeting or developing guidance documents, et cetera.

So that would be very helpful if you can come in early to give us your development plan, and then we can work through the specifics.

MS. MAURER: But if it's a situation where

you're receiving a fast track designation prior to -- just prior to your NDA filing, say a year or so ahead of time, where you've been working with an accelerated critical development, say under subpart E, or you hadn't worked (unintelligible) for example, is the agency looking towards postponing some of these standards (unintelligible) very long-term expensive studies such as carcinogenicity studies?

DR. ZOON: Again, I think we're looking at it in a flexible way because some of them it depends on the nature of the product and what the properties of that product are as whether you can or cannot look at it postapproval, which is what I think you're trying to say.

So some of these things I think really depends on what the data you have now are, what some of these issues are with respect to the product in having to manage that. So I can't answer specifically because there's a lot that would come into that.

MR. STRICKLAND: Dr. Zoon, we have 30 seconds.

Let me ask one important thing. We have a transcriber here. So this is part of a public record. And anyone who has questions, please use the mike. And also, can you spell your name for the transcriber in the

corner so she can get the appropriate spelling of your name for the record? And the same will be true of the presenters, if you can give copies of your presentation to me or to the transcriber. Thank you.

(Interactive satellite teleconference)

DR. ZOON: I would like to open the stakeholder presentation session. One, if you have any comments that either you didn't get to fax to Dr. Henney or you have other information -- if you have any other information or comments you'd like to submit, Dennis Strickland will be taking those. Dennis, please stand up. Dennis will be taking your comments, and we'll add them to the comments that were received at headquarters.

So overall, I think the presentation was -- my own personal view -- very good. I hope it was interesting and informative to everyone and also a good opportunity to hear from Dr. Henney and Ms. Suydam. So hopefully, we'll look forward to your feedback on how effective you think that type of communication is.

We have several people that are listed to speak here -- I guess it's this afternoon now, and first is Dr. Rob Garnick. He is the vice president of Regulatory Affairs at Genentech. Rob?

MS. ZIOBRO: We'd like to ask if you have a copy of your comments and remarks, that you give them to

Dennis or to our transcriber so that we'll have them for the record.

DR. GARNICK: Thank you very much. And I'd actually like to take the opportunity to thank the FDA, Dr. Henney, Dr. Suydam and you, Kathy, for the opportunity to have this meeting here. And it's really a wonderful opportunity for the stakeholders to provide information and prospective thoughts to the agency about how we as the regulated industry understand the provisions for FDAMA, the work you've been doing with PDUFA, and to provide some thoughts about how we could actually do a better job working together.

If I could have the first slide, please.

Some of the prospective thoughts that we have actually been considering and providing the agency with, some prospective and positive feedback is the thought of providing and creating technical advisory boards. This will consist of mixed boards containing mixtures of thought leaders from industry, academia and FDA who would recommend to the agency when important national issues need to be discussed in a very open and positive forum. I'm mindful of some of the very positive things that we've had from the biotechnology perspective in the past, the performance of genetic stability as well as a very important one on well-characterized proteins that

has led to a lot of forward and positive issues that actually have occurred under FDAMA, in particular with respect to fast track. These are really important areas, and at the time I am mindful of the fact that we have had mixed groups. But to codify this and put this into routine operation, I think it would be a very positive and forward-thinking approach for the agency.

This would create, I think, very importantly a climate where important issues that are on the forefront of concern from the agency, the public and FDA would be brought forward and discussed, and a very clear risk-based decision making approach can be used.

One of the issues that I think is very contemporary right now is the issue of generic biologics. This might be a good opportunity to consider the use of such a technical advisory board.

Next slide, please.

To answer the question that was asked on reciprocating exchange and integration of scientific information and agency scientists, I think one of the important areas that we might be able to contribute is the advice to hire and maintain experienced and pragmatic staff. And from this standpoint, as we know, many of the regulatory agencies around the world insist upon their staff having had actual industry experience.

And I can't say enough about the fact that experience in making risk/benefit decisions is a crucial area for us and that the agency really needs to think very clearly and carefully about the ability to hire experienced and pragmatic staff.

There's also the opportunity to provide for agency scientists' engagement in laboratory research. I think this is a very critical area. To be able to use the proper judgment to review the very complicated submissions that are being proposed today from the novel sciences that are being developed in the biotechnology area, it's critical that scientists have both the experience and understanding in order to make those judgments. We propose that sabbatical programs be created and that corporate internships be considered where FDA scientists could spend time actually in the regulated industry to be able to learn the state of the art that is being considered at those times.

We'd like to propose that scientists from the industry present state of the art symposia to FDA scientists and that potentially we use the technical advisory board as a forum to discuss new information, advise FDA and hold appropriate symposia.

Next slide, please.

With respect to educating the public on risks

and benefits, I think it's important to better educate the public on the basis for the approval of new medicines. As we've heard in the video conference by Dr. Henney and others, the public unfortunately does not understand the complexity of the drug development and approval process. And this leads to a lot of confusion and difficulties with respect to reporting adverse reactions and other problems, and for the FDA to take a proactive stance in terms of educating the public would be a very positive and forward-thinking approach.

This would provide the public with better information about the pharmaceuticals that they have been prescribed and also for them to understand the risks that are associated with the use of those pharmaceuticals.

And one thought would be to look at using the publicly supported forum like National Public Radio or television for patient education to have actual FDA fireside chats. I'm actually mindful of this presentation that we just heard and that having that on a national public television, I think would go a long way to having the public better understand the complexity of drug development and use of pharmaceuticals as well as how best to report adverse reactions when they're observed.

Next slide, please.

A very important issue I think as you pointed out is limited resources. The agency clearly is limited. PDUFA has gone a long way to improve the situation. But as we all know, it is still far from perfect. I think some of the ways in which the agency could use its limited resources in the most productive way would be to partner more actively with product sponsors, to use the advisory committees that are proposed, to establish priorities potentially for fast track products because we are mindful that, as we heard, under FDAMA fast track is a wonderful and powerful addition to our (unintelligible). However, it comes with a cost, in that not all fast track products have as high a priority as others. It is a difficult decision to make with limited priorities. I'm mindful of Dr. Henney's words that priorities priorities priorities are the most important thing before us.

It's also important, I think, to have FDA influence the sponsors with respect to what will actually help the reviewers to make their decisions the most appropriate way. FDA could actually sponsor a workshop that would focus on what reviewers want in terms of making their life easier.

And a final point is the inspection program.

I think inspections -- and having been in the regulated industry now for 22 years and having gone through literally hundreds of inspections, I would have to say that the inspection program, while very valuable, may be more important to be applied selectively rather than in a uniform way. The industry does go through -- spends enormous amounts of time on inspections, and not all of the industry are those that need to be inspected more frequently. And that the agency might want to consider an inspection policy where companies with excellent compliance and GMP history are perhaps not as heavily inspected as those who are nowhere near as compliant or have poor GMP experiences.

Next slide, please.

With respect to stakeholder communications, I think this has been an excellent venue, and I would like to encourage you to continue to seek the stakeholder input, that more and more frequent and early discussions such as these will benefit both the agencies as well as the industry, that we'd like to continue to develop and draft guidance and keep industry informed. And I would also like to reiterate that having the industry participate in the development of these draft guidance documents would, I believe, facilitate the development of these guidances and their acceptance throughout the

industry.

I think to implement modernization effectively and consistently, it's important to harmonize the guidance and process across the centers. At this time, while there is a tremendous value in development of this guidance, it is clearly not harmonized across the various centers of FDA, and this would be very helpful to the industry, particularly those who may deal with biologic drugs as well as devices.

To harmonize globally, I think the ICH process is a critical area. FDA has actually led the way in ICH, and this requires a lot of time and effort and dedication. And to continue to provide the horsepower necessary to facilitate the ICH process will make I think the entire situation very productive and positive.

Finally, there is the situation of pharmacopeia in that the regulated industry does follow the pharmacopeia and is highly involved with them, and they do provide very excellent guidance. I would like to encourage the agency and all the centers to work closely with pharmacopeia in defined areas where mutual partnership and value can be obtained.

In conclusion, I would like to say that I

think the agency has done a wonderful job implementing FDAMA. I think it has been a hard and difficult road to follow. But your clear wisdom and guidance and leadership in the area is appreciated by the industry.

Thank you.

DR. ZOON: Thank you. Thank you very much.

(Clapping)

DR. ZOON: Yes. If I could -- would you take a few questions for clarification? One of the things I would like to ask, when you talk about input into guidances, because of the federal advisory committee on some parts of this is a bit limiting both with the boards and with the ability to really formulate some of these things in an interactive process. And I was wondering -- I love the concept of these. Do you have some suggestions on how you think we could from the perspective, could it be workshops, in ways that we could do the interactions on the scientific issues that would lead into the documents?

And secondly, in looking at the technical boards, how do you perceive those to come about in some of the dilemmas we have with respect to other provisions that we need to comply with?

DR. GARNICK: It's a good question, and I probably don't have all the answers for it. But I

remember the well-characterized protein symposia that FDA began a few years ago and the value of that in which you actually had representatives from industry as well as FDA begin to think through and plan that type of meeting. That was a one-of, and it was very valuable. And I think the ramifications of what were done at that meeting we're still developing today.

But to codify this type of approach, the development of boards -- and I think you can have boards in the area of clinical studies, free clinical studies, and manufacturing and controls and potentially post-marketing safety. You could develop boards like this that would be standing. The membership could be chosen by FDA. For example, they would be publicized. People would know who are the members. They would probably have some rotation basis. But the challenge to them would be those picked by the agency so that when timely and important issues begin to emerge, and we all see them emerging, that you could be able to get the horsepower of those groups together to decide what the situation really is or isn't, whether a national symposia such as a well-characterized protein, what needs to be held in those areas and to provide you with the guidance in terms of where to go from there. And I think that would help quite a bit.

With respect to the requirements that you have with disclosure and things like that, I think we would have to work to find -- to work our way around that, but it clearly is possible to be done.

DR. ZOON: Thank you. Jerry?

DR. DONLON: I just have a few simple questions. One thing in the area of enhancing the science base for the agency or for (unintelligible) -- are there specific disciplinary areas or scientific areas that you recommend we pay attention to or root for or enhance?

DR. GARNICK: Actually, I think that from my own experience the agency does find people with good educational backgrounds. But it's the experience base that sometimes is lacking. There are a lot of excellent universities, but they don't teach you what actually happens in real life. And it's people -- I would encourage you to find and hire people who have had experience and who know -- or are more pragmatic in their approach and judgment. And some of the areas in which you might be looking in I think in terms of chemistry, chemistry, biochemistry, clinical trial design, pharmaco (unintelligible). These would be important areas to focus on.

DR. DONLON: Would some of the emerging

technologies in pharmacogenetics, things of that nature, should we be looking to enhance our abilities in those areas as well?

DR. GARNICK: Absolutely. I think there's quite a lot of work going on now in the areas of cell and gene therapies. And this is clearly an emerging technology which there are very many new things that need to be discovered and dealt with. And there are a lot of interesting and complicated regulatory aspects to them.

So looking for people in those areas I think would also be very valuable.

DR. DONLON: Brief question: You mentioned inspection program, the need to perhaps modernize the inspection program in a way. There is an initiative clearly with the foods and the seafood issues by looking at the pass -- applying passive analysis and critical control points type of programs, and devices is looking at piloting that into the device area. What's your sense as far as industry's reception to that type of an approach more broadly in the biotech industry?

DR. GARNICK: With respect to the biotech industry, I think to put it in perspective, this is a new industry that people who are involved I think are extremely serious and dedicated to the development of

new products and (unintelligible) mode. They are particularly mindful, I believe, of FDA guidance and interactions, and they probably are the most inspection-conscious members of the industry. That may or may not be true in all cases. But in general, they are probably very highly inspectional -- inspection concerned and experienced. And they're probably not the problem. The problem may well be elsewhere. And to spend enormous amounts of precious FDA resources, particularly with respect to the new BLA process and under fast track where inspectional issues as well as issues with response to the submission are actually being reviewed, it's probably not the best use of FDA's time. I would concentrate my efforts where the problems really lie, and I think you know from your compliance and GMP experience exactly where they are.

DR. DONLON: One other observation. You mentioned we should have a closer working relationship with the pharmacopeia. I just want to point out that Dr. Kenney is past president of the U.S. Pharmocopeia.

DR. GARNICK: Yes, I am quite aware of that. I think she has gone a wonderful job in that area. I would really encourage the pharmacopeias and the FDA to find a harmonized ground in which real value could be added to the industry.

MS. ZIOBRO: Thank you. I'd like to ask our next speaker to come up, Cindy Morrow, who is the senior regulatory specialist at Becton Dickinson.

MS. MORROW: Hello. My name is Cindy Morrow, and I'm an employee of Becton Dickinson Biosciences in San Jose. I wish to thank the Center for Biologic Evaluation and Research for providing this opportunity to share our suggestions for FDA's efforts to improve its implementation of the law. I'd also like to thank my mentor and boss, Anna Longwell, who helped me actually prepare these comments.

First, I would like to address some ideas of how FDA might expand its capability to incorporate state-of-the-art science into its decisions.

CBER is noted for its commitment to biologic science. From the origins at Treasury through its long (and continuing) association with NIH, CBER has been committed to understanding and contributing to advances in pharmacology and molecular and cell biology. However, now CBER must also review devices, ancillary products and combination products, which require additional expertise in such varied disciplines as computer science, polymer and surface chemistry, and many other technologies. We suggest that CBER work more closely with the other FDA centers to acquire this

expertise.

Please take advantage of the resources you already have within FDA, but perhaps use them differently. Also, get more advisory committee members with expertise in the physical sciences and computers. You could also ask manufacturers to provide more information about the basic science and technology involved in the development of their products well in advance of product review.

A vendor day is a technique employed by other centers to gain knowledge and allow interaction with industry. This idea could be expanded to a more science-fair-like event, to include discussions on areas of mutual interest for industry, regulators, and the public and provide opportunities for hands-on demonstrations of technology, including instrumentation, hardware, software and product information.

It's important that FDA management provide the time and resources to allow all levels of FDA employees to participate in learning opportunities in order to encourage and maintain the good people that you already have employed at FDA. In your hiring, seek out individuals who have both scientific expertise and experience in the practical application of medical products. Look for opportunities for reviewers and

investigators to participate in externship programs where they can gain experience with medical products and the practice of medicine.

Next I would like to address how FDA might incorporate state-of-the-art science into its risk-based decision making especially in the area of new product reviews.

We all acknowledge that the rate of scientific discovery and development is accelerating. Under today's product development systems for biologics, or for devices reviewed by biologics, any truly novel product reaching the U.S. market will be at least one generation (or more) removed from state-of-the-art. However, this situation can be beneficial.

An extensive program of design and testing is not only a regulatory expectation but has become an industry (and indeed a public) expectation for any truly novel health care product entering our market.

One result of this careful and organized approach to product development and evaluation, combined with the almost daily changes in technology and science, is that no product will be state-of-the-art when it reaches the reviewer's hands. If the FDA insists on "state of the art," companies are continually thrown into a round of revisions and validations for each

significant improvement. And products that will have significant health benefits for patients and their providers will not reach the market in an appropriately timely fashion.

FDA should not feel that it alone has to provide incentive to manufacturers for continual product improvement. For high-technology industries making regulated product, there is ample incentive to continue state-of-the-art product development. Our competitors provide this incentive. For most of us, the motto is "improve or die."

In review, FDA should principally base its expectations for product performance on what is currently available for use in the U.S. market, not on what is being explored at the NIH or other world-class research institutions. Risk/benefit assessments for marketing permits should not be conducted on what could be developed, but on what is currently available.

For issues concerning product safety, FDA should base its review on the very latest information, as long as that information is based on labeled claims for the products, statistically valid scientifically sound studies, and is not anecdotal information, whether obtained from peer-reviewed scientific journals or other sources.

One use of state-of-the-art science which in the assessment of risk for which FDA deserves commendation is their consideration of new surrogate endpoints for clinical studies and new in vitro analogues for lengthy animal studies. These advances in science serve to shorten testing time and allow innovative products to reach the market sooner, thus shortening the product life cycle while still protecting the public health. We expect FDA will continue to encourage advances in these areas. By encouraging more scientific ways of establishing product performance, FDA will also assure that the product reaching the market is as close to state-of-the-art as it can reasonably be expected.

When there are scientific disagreements, we recommend that FDA have available mechanisms to take the issue to an outside scientific review process, short of convening an advisory committee. However, yesterday, I ran across a new CDRH draft guidance on resolving scientific disputes concerning the regulation of medical devices that I'm looking forward to reviewing. I just had a chance to print it out. It showed up on the Internet yesterday.

Next, educating the public about risk/benefit analysis. Risk/benefit analysis is not well understood

by the general public. We see this frequently, when the news of a single disaster with a product outweighs the years of positive health effect obtained by use of the same product. News stories about disasters command attention, while statistics do not get the same coverage.

If the FDA wishes to provide outreach to the general public about risk analysis, we suggest an approach that might utilize the Internet to capitalize on some more familiar risk/benefit choices that people have to make every day. It might be possible to utilize FDA's Office of Special Health Issues home page to develop an outreach program that explains risk/benefit analysis in simple terms.

The approach might provide examples of what people have to consider when evaluating their own medical treatment options with the help of their physician. For example, what questions they need to ask their doctor and risks and benefits associated with each treatment option. This might be done for key diseases with three or four alternate therapies to help explain the concept of risk evaluation. Then, once the basic idea is established, you could explain how the same techniques are employed by FDA on a more global scale to review therapeutic or diagnostic products aimed at the

same disease categories.

Also, it would be helpful if you could convince nonprofit organizations interested in public health issues to provide a link to this same web page. It would afford greater public access to alternative points of view.

Next, improving FDA's focus. In this era of restricted funds, more cooperation between centers and between government agencies seems indicated.

If FDA wishes to concentrate more resources on areas of greatest risk to public health, we suggest close cooperation with the Centers for Disease Control, which has long been developing information on public health, and on our most serious public health problems. Once areas of greatest public health risk are agreed upon by FDA, they should be published, and a mechanism for updating these findings should be established. FDA might then consider expanding the Accelerating Approval process to include products which are employed to treat, diagnose or prevent these identified public health problems.

Additionally, CBER should work with industry to actively identify and downclassify lower risk devices that have a good record for safety.

Also, CBER should work with the CDRH to

standardize and clarify the "least burdensome" provisions of FDAMA relating to device review and clearance to market.

Cooperation between centers is now being attempted more frequently, and we applaud FDA, especially CBER, for their efforts in this area. We believe that more could be done to tap inter-agency and intra-center expertise in the areas of device review, web page design, and communication about processes in general.

Finally, enhancing public feedback for FDA communication efforts. We believe that CBER should make better use of its website to obtain feedback. Also, we believe that the website could be updated more frequently and be more transparent in its use. For devices in particular, it would be helpful to provide linkages to relevant guidance developed by CDRH. Just yesterday, I found a Federal Register notice listing guidance documents that were issued by CDRH that apply to medical devices regulated by CBER. That was published on Monday on the website. So you mentioned that. That's very helpful, especially if this information can then be incorporated into your website with links.

To obtain public feedback on particular

topics, it might be possible to post questionnaires to the website with "fill out the blank" type forms that could be returned via electronic mail. However, we have found at Becton Dickinson that many people are unwilling to give completely honest feedback especially internally unless they are assured of anonymity. Therefore, it might be a good idea for the FDA to contract with a third party and have them analyze the report on feedback to questionnaires.

We believe that local grassroots groups such as the OCRA group in L.A., the Orange County Regulatory Affairs, discussion group; the PAIR group in the Oakland district, Partners on Industry and Regulators; and IVD Roundtable, for example, in the Baltimore area should be supported and that more districts should be encouraged to form outreach groups with local industry. These provide for valuable interaction and feedback from members of regulated industry to regulators, and vice versa.

One area in which more feedback could be solicited is in the development of internal procedures and processes to implement FDAMA at CBER. We hope that CBER will allow greater and earlier stakeholder participation in the development of FDAMA implementation procedures.

Thank you.

DR. ZOON: Thank you very much. I appreciate all those comments. Any clarifications? I think it's clear.

(Clapping)

DR. ZOON: I'd like to ask Paul Holland, the last scheduled speaker, to please come up. Paul is from Sacramento Medical Foundation Blood Centers.

DR. HOLLAND: Thank you, Kathy. I'd like to thank the FDA for holding these sessions. I think they are useful. I appreciate the ones you have had in the past and that you've provided us feedback from those. I think that was very helpful to us all. I'm disappointed and dismayed that more people from blood banking and transfusion medicine, my field, are not here to comment or at least attend. It's a great opportunity to provide your input.

In providing my comments today, I hope you'll take them as constructive comments, that they are from our own center, my staff, and not from anyone else. I tried to organize them in response to the questions, and so I'll go through them.

The first one is what actions do you propose the agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based

decision making?

Implement your own quality assurance guidelines -- these were issued in July of '97 -- and put them into your labs and processes at the FDA. They apply to us, and I think they should apply to you, too.

Certainly if you adopt a systems approach to FDA's own quality system and operational areas, such as the ISO 9000 model, incorporating principles of continuous process improvement, tracking and trending, et cetera, I think that will help you.

We certainly support your goals of maintaining firsthand scientific expertise on relevant technology and diseases. But you need to supplement with experts or by partnering from various fields to expedite evaluations of new applications of old products and the requirements for, in my case, donor blood testing.

You can certainly access outside scientists and medical experts. As was said in other ways, I think you might have a scientific advisory committee. You have a blood products advisory committee, but today this has few scientific blood banking transfusion experts on it.

I think you need to perform risk assessment based on true hazards or harmful incidents, not just

every GMP violation. The FDA has made extra work that has nothing to do with minimizing harmful risks.

You need to identify errors that present known harmful risks and require only those to be FDA reportable. For example, these would be FDA reportable: A true infectious diseases reactive unit that was issued; a contaminated unit that was issued; untested unit issued; ABO/Rh mislabeling. You really need to minimize FDA reporting to critical issues.

Use scientific evidence (by expert consensus) to establish new regulations.

Please do not implement precautionary measures without known fact or cause/effect impact that will decrease the donor or donation rates, and by how much. Eliminating eligible donors on speculation or just theoretical possibilities can result in lack of an adequate blood supply, and this could actually result in real patient death, very directly.

The next question was what actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities throughout a product's life cycle?

A specific example: Reconsider the need to continue the requirement for submitting products for

platelet quality control. Are any discrepancies and perceived failures in counts at CBER due to equipment differences, modes of use? Has this been scientifically investigated? If the facility producing these platelets has adequate data to show the required criteria have been met, why continue this requirement on only this one product? What is the real public health risk? Is there one? The requirement is costly; it uses up a valuable component that patients cannot receive. And we really wonder how meaningful this process is.

We think you should establish a hotline, fax line, Internet page, whatever, for the regulated industries to obtain quick answers to questions from an identified pool of FDA subject matter experts. This would really enable greater collaboration with FDA in bringing new products to market to benefit patients. For example, my area again, licensed pediatric platelet dose, a blood product, to streamlining submissions and clarification of new processes coming, like the BLA (Blood License Application). We need to work with you on such issues as a comparability protocol, monographs for standardized blood products, and pilot programs for licensed blood products (like irradiated blood pilot) that you produce.

Again, echoing comments of other speakers,

establish public forums and workshops at national meetings with scientific information presented. The FDA must take quicker actions and finalize documents more quickly. Some items, like the product license applications, are approved after the blood center has moved on to new methodologies. We are no longer using the methodology anymore, and we finally get them approved.

We think you should do away with PLAs all together, product license applications. If a center validates and meets the criteria of regulations, why not allow the product to move in interstate commerce in that basis.

We would appreciate if you would finalize some of your draft guidelines a little more quickly. As an example, the draft computer guideline is years old, and it still hasn't been finalized.

Question No. 3 was what actions do you propose for educating the public about the concept of balancing risks against benefits in public health decision making?

I think you need to provide analogies with real-life risks that are undertaken daily. That is, how does the risk compare to driving a car, flying in a commercial airliner, riding a bike, walking up stairs?

This approach would really, I think, assist the public in gaining a perspective on risk-related issues that are often very emotionally charged.

Question 4: What actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?

As I said, that's another answer, is really streamline your product licensing for standard blood and blood products to a monograph system of basic specifications.

Echoing, again, the comment I made before, eliminate the need to submit actual platelet products to be sent to CBER for quality.

On site inspections and overall enforcement via reporting of errors and accidents and recalls focus on minute details, not usually the overall system, or real risk to transfusion recipients. A systems approach to both would allow delineation of isolated events, from true system-wide issues that need to be addressed in a much larger context.

We wish you would require that error and accident reporting and recalls only apply to issues that pose real risk (by some predefined criteria) to the public. Some of the errors and accidents we have to report are GMP related only, and almost all donor

accidents from post-donation information are low risk or have such low potential such as potential malarial exposure travel, subsequent illness. You and we need to focus on higher risk issues for the biggest benefit of the public and really require only reporting if the data are used for some follow-up purpose. Just to gain this data without using them doesn't help any of us. What do you do with this data other than making internal reports? What is it used for? How is it used? I think we need to have you and us have use of that.

We suggest to set a timetable for updating all blood and blood product regulations and fold them all together in one set, incorporate all the previous FDA memos that are endorsed into regulations.

Make the regulations in the CFR available on the Internet with a search capability by topic and cross-referencing to related topics.

We really appreciate your efforts, but we need you to continue to work on decreasing and eliminating the paperwork burden for reporting and licensing. The annual report is one example of additional new reporting requirements that have a significant increase in data handling and reporting to CBER. The new BLA and form 356h will require more data and information to be submitted for product licensing

than the previous process required.

You need to revise the recall regulations to provide more specific criteria based on real risk, for required notifications and recall, and follow-up on the disposition of products. This action would decrease the amount of activity now required for many low risk recalls, which most of which are just GMP breach only.

We would appreciate if you would plan the public meetings on new regulations, new guidance documents, new proposed programs to be bi-coastal or via satellite downlink (unintelligible) such as today. Due to the distance and travel expenses, we cannot send a representative to a one-day meeting in the middle of a week on the opposite coast.

FDA assessments of fiscal impact and are often totally unrealistic in proposed documents and, we believe, largely unfounded. We need to have you base these on real data, please.

As a plea, we'd like you to address, up front, the reimbursement issues of blood centers and hospitals for FDA mandates or recommendations for testing, or product manufacturing, or strongly support new research testing, such as H.I.V. antigen, Nucleo-acid testing, (unintelligible) blood products. We need you to help us, and you need to notify and

encourage HCFA about adequately reimbursing us for added costs of FDA mandates and recommendations. We too have budget limitations, and we cannot do more with less as you've heard.

Most blood centers and hospitals are not for-profit. The decisions for new requirements must include how they are going to be paid for.

We'd appreciate if you would eliminate unnecessary activities such as recalls that will not provide a beneficial outcome or prevent harm. Many recalls and component retrievals are useless in really reducing risk.

As was mentioned by one of the speakers, there is a coalition for regulatory reform, CFRR. The blood banking community tries to get its comments and concerns in to them and from them to you. But often, they don't seem to have much weight. We are often told that CBER wants to hear individually from centers and from individual people, not the CFRR. We rely on the CFRR to represent us since most of us cannot send representatives to meetings that CFRR would attend.

Question No. 5, what actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?

I think some written surveys to stakeholders seeking input on top of some questions would be worthwhile.

We need you to provide feedback from these surveys or meetings by the Internet, written reports, whatever.

Setting up an Internet page for a dialogue/feedback on topics or on defined questions that change on some regular basis would be of help.

Set up a mechanism for error and accident reporting via Internet with encryption preferable.

The new FDA annual report notification of changes process has added pounds of paper work for blood centers. What good is this doing to protect the blood supply or for the center? FDA inspectors can inspect for any and all changes they want during reinspections. What is the value of submitting all this input to help you? Parenthetically, we can't really digest it all.

Having inspectors review product validation on site. Can the FDA really manage all the reports it gets and in a timely manner?

In general, the comments I'm trying to make are that we really need help from you. We need to help you. No doubt about it. And one of the areas is that when we ask for advice or questions, we would like a

concrete and specific answer, preferably in writing. So often we get an answer, "that's under review," or "that document will be out soon" or "we're here to help you." Without something in writing in a specific response, we are not helped a great deal. And it should be based on the current regulations. And hopefully, it should be a quick response.

All of your biologic regulations need to be updated. Many are archaic. Put them all in one section. Resolve discrepancies between the CFR and FDA memos and guidelines. We need you to take the words "just do it" just as we have to based on scientific information from expert consensus. And if there is no consensus, then I'm not sure we should have such regulations.

Our final plea is basically to consider risk in general. I thought one of the most valuable things I learned today was a comment by Dr. Henney. She said "Safety does not mean there is no risk." And we are working harder and harder and spending more and more resources on making the blood supply safer and safer, when we might think that our tax dollars might be better spent on societal issues such as smoking, drugs, guns, poor education, lack of medical access, underage drinking. These are really more worthy topics than

trying to further minimize the small risk we have from the blood supply, which is extremely safe today.

In closing, once again, thank you for the opportunity to make these comments. If you have any further feedback, please, I am happy to answer them, or my staff, especially Sally Morgan-Gannon and Sallie Holliman, who helped me write this statement.

Thank you.

DR. ZOON: Thank you, Paul. One question that I'd like to ask you is do you think the blood -- in hearing your comments, many of the objectives that we have put forward in the blood action plan, there is a lot of overlap. And my sense is in your review of that, do you think that captures a lot of what you're trying to do? Because that's where we are right now.

DR. HOLLAND: I think it does, but I think we have to get on with it. We have to get to it and do it. And some of these suggestions we both agree on; we just need to do them, because it will eliminate your unnecessary work, allow you to have better use of your limited resources, as would be true for us, too.

DR. ZOON: Thank you. Do you have any comments?

DR. DONLON: Just one observation. You were commenting on the quality assurance practices. The

agency is initiating an evaluation of a proposal basically to accredit the laboratories in the agency, to accredit them to the ISO 25 or ISO 17025 version of that, so we are moving in that direction. And our center certainly, I think, has taken the lead in that regard. So we are recognizing that we know it's appropriate for industry, certainly appropriate for our laboratories.

DR. HOLLAND: Great. I applaud that. Thank you.

DR. ZOON: I might also add we had an external review of our entire science program at CBER last year, and one of the recommendations that we have started implementing from that external review was to increase the quality assurance program at the center and with respect to private testing.

So those recommendations have been made and instructions to each of the offices to -- as resources permit, to start implementing that recommendation. I think the findings of the plan is being drafted as we speak.

So I think that's very timely and very much on target with the external review. So thank you for those comments.

DR. HOLLAND: Thank you.

(Clapping)

MS. ZIOBRO: I'd like to ask now, do we have any comments from the rest of our audience here?

Margie, would you please come up to the microphone, state your name, who you're with, and spell your name.

MS. VASILEVSKY: Okay. My name is Margie Vasilevsky. That's spelled V-A-S-I-L-E-V-S-K-Y. And I'm with Bayer Corporation. I'm a QA manager, and I'm also on the (unintelligible) steering committee representing biologics. On this issue I am representing the West Coast chapter of ISPE.

And the issue is that we would like to participate in a rewrite of the 1987 process validation guidelines. We have an advisory board, industry executives, and they overwhelmingly said that their biggest concern is out of control cost as it relates to validation. And we looked into this, and it seems to be the consensus of the industry that there's been an incorrect emphasis on validation, non-value added versus value-added activity. We would like to see it go back to scientific principles that really insure product quality. For example, 80 percent of our time, generally speaking, is spent on IOQ. It should be the other way around. We should be spending 80 percent of the time on

PQ and on process validation.

So that is -- I just had that one issue.

DR. ZOON: Thank you.

MS. ZIOBRO: Anyone else?

Kathy may be able to make her plane now.

DR. ZOON: Thank you very much.

I just want to say it is a pleasure to be here. Sometimes when you're sitting here and listening to the comments makes you feel a little bit bad, but I know they're given in the right spirit. And we take them that way. So I thank you for that.

And if we all can sit and discuss it in a good old-fashioned honest way, I think we will make progress. And we do appreciate that.

I would like to thank everybody who spoke up today as well as those of you who have been considering jotting something down to please do so. I really encourage you to because that's the only way we'll really know where your concerns are. We will do our best within our resources to be responsive.

I do have to say, especially in the blood area, that has been a problem that we're facing in our resource areas. So we really -- to the level that you can help us, give us your priorities as what needs to be done first, that's always very helpful. We ask the same

question to the device industry as well, because of the limited resources we have, what is most important to do, so that we can make sure that we're targeting the right things in the right order at the right time.

So to all of you who have come, I want to personally thank you. I appreciate it. And you don't need to just wait one time a year to give us your feedback. I think we're willing to accept feedback any time during the year. And our Office of Communication and Manufacturing Assistance with Dennis Strickland, who is here, can give you information to get word back to the agency and CBER on any issues that you might need.

I would also like to thank our host, San Francisco District. Thank you so much. And we really appreciate it, Pat. And for all your hospitality.

MS. ZIOBRO: And as you suggested, Dr. Holland, we would really like to continue having bi-coastal meetings such as this because that's where the bulk of the industry is. So we appreciate that.

I'd like to remind you all to fill out your evaluation of the teleconference because what we hear from you today will govern whether we have more of these. And I think we all agree it was a real beneficial experience for all of us.

Is there a need for anybody to return after lunch? I see us at a point where we've run out of comments. If you feel you would like to come back for a discussion, we can do that. Is there anybody who feels they would like to come back and have discussion? Okay. Because we want to do what you want to do.

All right. I think that will be the end of it. Again, thank you for joining us. We'll see you again soon, I hope.

(Proceedings adjourned at 12:56 p.m.)

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I, CLARE MACY, a Certified Shorthand Reporter, hereby certify that the foregoing proceedings were taken in shorthand by me, at the time and place therein stated, and that the said proceedings were thereafter reduced to typewriting, by computer, under my direction and supervision;

I further certify that I am not of counsel or attorney for either or any of the parties nor in any way interested in the event of this cause, and that I am not related to any of the parties thereto.

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