DPEARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICE ACTION PLAN

OPEN PUBLIC MEETING

9:00 a.m.

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National Institutes of Health
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AGENDA

P R O C E E D I N G S

MRS. EBERHART: Good morning. My name is Kathy Eberhart. On behalf of the agency I'd like to welcome all of you to this open public meeting on the Medical Device Action Plan.

We have a pretty full schedule today. We're going to have a break this morning after, I believe, the first four speakers, and then we have lunch I think around 12:15, as you can see on the agenda in your folder. Then we're not sure how long the afternoon's going to go, so we're just going to have to play it by ear.

The bathrooms are out in the hallway this way and there's a cafeteria in the building for lunch. And if you have any questions, please feel free to ask me any time or ask anybody that has a name badge on that's with the FDA. And if you need anything, just come out to the table any time during the day and we can help you.

We do have a transcriber, as you can see, and if you would like a copy of the transcript, we have the address to the FOI office out on the table, also, if you'd like a copy of that address.

I'd like to welcome our first speaker today. It's our Center director, Dr. Kathy Zoon.

OPENING REMARKS

DR. ZOON: Good morning. I would like to welcome

everyone and thank everyone for coming today, especially a number of our speakers who have traveled long distances to be with us.

This is a very important meeting for CBER. It's important for many reasons. One, I think it reflects the spirit of some of the negotiations that we had on the FDA Modernization Act, with going out, reaching, listening to the public, hearing what the public and our constituents have to say and then responding to those issues in a way that we can further understand and then have a plan to deal with the problems that we face.

One of the issues, and you'll hear today--I'm going to give a brief overview on the CBER Medical Device Action Plan and a number of our colleagues from the Center will be presenting today, but I think it's very important for us today to have an opportunity to hear from you, hear from those of you affected by the FDA and our processes and how we can make our processes better and more effective to serve the public health.

In doing this, I would like to start out by just reminding everybody of CBER's mission statement. Our mission is to protect and enhance the public health through the regulation, the biological and related products, including blood vaccines and biological therapeutics, according to statutory authorities. The regulation of these

products is founded on science and law to ensure their purity, potency, safety, efficacy and availability.

And to the extent that CBER regulates devices and their impact on blood safety and other products that we regulate, this is a very important part of our program. It is a relatively small part of our program but one that we take a lot of pride in and I think one that we are seeking advice from you, who are affected by us, to do even a better job.

If I can have the next overhead, the principles for the regulation of all biological products, and these include our biological devices, involve a number of fundamental principles. They involve our review capability, our research capability, our ability to understand the science behind what people are doing and trying to enable that science to bring forth products, surveillance, policy development and compliance.

All of these are very key and important components in the regulation of biological products.

The next overhead shows you the range of products that are regulated by CBER. They go from tissues, whole blood, blood components, blood derivatives, vaccines, allergenic extracts, monoclonal antibodies, biotech-derived therapeutics, somatic cell and gene therapy and zenotransplanation. Devices cross-cuts many of these

product areas and therefore we have active participants in our Center involved in this.

We have taken an opportunity in looking at our device program and have actually worked very closely with our field colleagues, as well as CDRH. John Stigi, who from CDRH was supposed to be here, couldn't make it today because of a personal issue and we're sorry he's not here but they have been very active on our committees, which we will explain to you today.

So we're really very much trying to look at our device regulation in the broader context, looking at FDAMA, looking at its implementation and how it relates to biological devices.

The next overhead gives you some of the examples of devices reviewed by CBER. In this case our primary products include in vitro test kits and related instruments, blood collection and processing devices and blood establishment computer software.

Many of you in the audience, we have worked very closely on a number of these products with you and we are anxious actually to hear from you or your representatives today in some of the issues surrounding the review of these different classes of products.

The next overhead shows you the level of effort that is currently being expended in device regulation as of

FY97. For the Center, and this includes all our product areas, the total level of effort is about 52.7 full-time equivalents.

This is important for you to know and it becomes even more important in the context of some of the current budget issues that the agency has been facing over the past five years. We've had a decrease in resources for non-PDUFA programs by virtue of annual reductions and Mr. Elengold will be presenting some of the budget information to you in the next presentation.

But I think it is fair to say that our non-PDUFA programs have really been challenged to have the performance levels even equivalent to what we had in the early '90s in order to do a number of the reviews.

The next slide shows some data on the number of PMAs and PMA supplements that have been received by the Center and are pending and those that are completed. This represents data since 1992 and as you can see, in 1997 there was quite a large receipt and pending number. That has come down this year. Over the past several years many of these issues are being managed, but I think we still have some work to do.

The next slide looks at the data for 510(k)s. I think it's self-evident what the data says. I think what this data says is that we're still struggling to keep up

with the workload that we have regarding the review of submissions. I think we're making progress. As you can see, the received and pending is coming down and the completions are up a little bit in '98, but I think there's still a differential that we're challenged to take care of.

The next slide shows the completed device reviews versus the FTEs. I think there's been some increases over time. This is just for the Office of Blood Research and Review and doesn't include Office of Compliance, Biologics, Quality and Office of Therapeutics. It allows you to see that.

For to past three years we've tried to at least maintain the number of FTEs in the Office of Blood in order to deal with device reviews to the best of our ability, even within declining resources.

The next overhead talks a little bit about FDA modernization. Many of you are familiar with this in the audience but this law was signed into effect in November of 1997 and CBER has been very much a very active player in the implementation of the FDA Modernization Act.

Clearly we're affected by many aspects of this act, both for our new biologics and drugs, our devices, and our policies and procedures as they are affected by this particular act.

We have been in contact with CDRH as it relates to

devices since the FDA modernization. Dr. Jerome Donlon has been our liaison to CDRH in participating in the guidance and regulation development as they apply to CBER's products. We have been very much actively engaged in that process.

Now, there are some things unique to CDRH in this legislation and some things that do affect the Center for Biologics and we are working very closely with CDRH and are going to increase our interactions with CDRH as we go forward and develop the Device Action Plan.

The next overhead, as part of FDAMA, was to do outreach and CBER was very active in the 406(b) initiative of FDAMA to reach out. We actually had several meetings, two of which were CBER alone, one on the East Coast here in Washington, D.C., one on the West Coast in Oakland. And then we also did a separate meeting with our colleagues at ORA out in Irvine, California and we also participated in the broader FDA 406(b) hearing in September in Washington.

I think this was a very important process for CBER. Many issues, especially in the device area, were raised.

And if I can have the next overhead, some of the themes that we heard in these meetings were the following: industry's general dissatisfaction with CBER's regulation of medical devices, concern that device review standards are not harmonized with CDRH, improvements were needed in review

performance, improvements were needed in communications during the review cycle, and CBER field requirements were not coordinated.

These were very serious things that we heard and we took these comments very seriously.

As a result, if I could have the next overhead, CBER took a number of follow-up actions. We established a device core team, which was co-chaired by Dr. Jerome Donlon and Dr. David Feigal. This is actually an intra-agency group that includes individuals from CBER, CDRH and ORA and Team Biologics, addressing some of these issues that were raised at the 406(b) hearings.

Dr. Donlon this afternoon will be giving you an overview in a general sense of our draft plan to deal with the issues that we heard.

But more importantly, we're very much interested in hearing if we got it right and hearing if the issues that were raised are the issues that are important to you, what are some of the suggestions you may have to help deal with some of these issues, and to move us forward.

As a first step to that, we have today this open public meeting to discuss the draft Device Action Plan, to open the dialogue, to get your thoughts and your ideas so that as we develop the action plan, we can make sure that it truly reflects what the issues of importance are.

We look forward to this meeting. We look forward to hearing from you and we look forward to working with you over the next several months in order to fully develop this plan.

So as a result, we have no preconceived conclusions. We come here to listen. We are open to constructive input and proposals and we look forward to working with all of you that have an interest in devices now and in the future.

So with that I want to thank you very much and I appreciate you all coming today.

I now have the pleasure to introduce Mark Elengold. Mark is the Deputy of Operations for CBER and he will give an overview on budget and Team Biologics. Mark?

BUDGET ISSUES/TEAM BIOLOGICS

MR. ELENGOLD: Thank you, Kathy.

It's also a pleasure for me to be here and I want to thank everyone who has come. We have a turn-out that's a little larger than we had anticipated but that's very good.

I also want to make a point of thanking the staff, particularly of OCTMA--Kathy Eberhart here who's running the slides, Gail Sherman, Laurie Harrison--for putting this together on a relatively short timeframe, with the assistance of folks from our Office of Compliance and Biologics Quality and particularly the Office of Blood

Research and Review.

We came to this process after the grassroots meetings, as Kathy said. We had the grassroots meeting here in August and Emily Rossiter and the Massachusetts Biotech Group had some comments about devices. Then two weeks later in Oakland there were many more pointed comments about devices. And finally at the Pacific Region grassroots meeting, which was attended by Laurie, me and Elaine Cole, who'll be speaking later and is the chair of the Biologics Field Advisory Committee in the Office of Regional Operations, it became very clear that something needed to be done to address the issues, ranging as simple as communication to as complicated as our processes.

So we came up with the idea for a plan. We wanted to make sure that we heard from people who were telling us there were problems that this was the right plan and in a relatively short period we put together this meeting.

There will also be a docket that will be open for a few weeks after this, so we'll talk about that later in the meeting. Your comments are encouraged to that docket. After hearing what we say today and you go back to your offices and your clients, discuss this with them and get their feelings on it and that's a very important part of this.

I've got the bad news/good news presentation here.

The bad news is our budget situation. Since we want to avoid anyone taking much time telling us we should throw money at the situation and fix it, I'm going to go over some numbers that show that that's not a way to do this. The only thing we can do, in the words of Gilbert's pointy-haired boss, is work smarter to fix it.

So let me just go over some of the budget issues. About four years ago CBER conceived a strategic plan and all of our activities and our budgeting and priority-setting processes are based on the strategic goals. I'm sure many of you have seen this before so we'll go over them real fast.

A managed and integrated regulatory process from discovery through post-marketing. A high quality research program which contributes directly to the regulatory mission. A high quality and diverse work force. Interactive information systems and leveraged resources.

This is what we're dealing with. This is the slide I refer to as the flying wedge. The area in red is our actual budget and appropriation figures. The black area to the top is what would be necessary to keep activities at the levels they were at in FY95.

As you can see, every year our appropriation, while it has increased marginally, was not adjusted for current services, increased costs, inflation, increased pay

raises. So even just to do what we did in 1995, we would need almost a third more funds than have been appropriated for this year.

Where's that money coming from? Well, if you look here you can see the bottom bar is our non-PDUFA salary and expense base. The bar above that is our PDUFA Prescription Drug User Fee Act base. The red area above that is our PDUFA additive, paid for by the prescription drug user fees. And the yellow bar at the top is other, and you'll notice that that's been increasing in size consistently, and that's implementation of that leveraged resources goal in our strategic plan--obtaining grant monies from other organizations, entering into CRADAs with Partners for Development, IAGs with other government agencies and areas like that.

The total CBER allocation--again you can see the pressure we're under and going back to the wedge, each year, because of federal government pay increases and the natural tendency as an organization matures, promotions to occur, has become a consistently larger portion of the money we have available squeezing the operating dollars. The money for computers, for contracts, for animals, for research, for everything we do, including travel to accomplish that, gets smaller and smaller out of the same piece of pie.

FTEs--when I started with the federal government

28 years ago we had man-years. Then we had staff-years and now we have full-time equivalents, representing the fact that we have many more part-time and job-sharing employees in the government.

As you can see, the number increased slightly back to FY97 and has pretty much leveled off since '96. Again you can see the vast majority of the full-time equivalent positions we have are in PDUFA because remember that PDUFA money is additive and the base level that we're required to maintain is equal to it.

Our operating budget--well, you can see that since FY94 it has gone down. And again the S&E portion has gotten smaller each year while the other portion, aside from FY94, which had some special fees in there, gets to be larger over time.

Our funds again you can see have gone down consistently since '94 and, most importantly, since there were some comments at the FDA meeting about CBER's research program, you can see that it's decreased by almost half since FY94.

Now to the good news. Now that I've shown you that we can't just throw money at the problems we have in devices, one of the things we've been doing to address some of the concerns is going to a new inspection and compliance system called Team Biologics. This is designed to conserve

resources and be more consistent with the rest of the programs in the Food and Drug Administration. And I assume most of you have heard the 20 or 30 talks that Elaine Cole, Jerry Vince, Debby Ralston and I have given, so we'll go through this kind of fast.

It was a plan for reinventing our ability to optimize compliance of the regulated biologics industry. It's a joint effort of CBER and the Office of Regulatory Affairs, which is our field organization. It uses the diverse skills of both groups and it focusses on inspectional and compliance issues.

It changed the responsibility for the biennial inspection lead from the traditional CBER employee to a field employee, and that was done to reduce inconsistency with other programs, including the CDRH inspectional programs. We have a cadre of specialized inspectors and inspections include a lead investigator who's a member of our core team and a CBER staff member, who we call a products specialist, and they receive specialized training in our industries.

It standardizes the traditional inspectional role that ORA performs for the other centers.

The core team composition is 12 investigators, one at least I see here, four national experts--oh, I see a second one; thank you--four national experts who are the

biologics national experts, who also report to ORA headquarters, and two compliance officers, one of whom I've seen here so far today.

They're located in the field offices around the country but they report to the ORA headquarters staff in the Division of Epidemiology and Inspectional Operations. Is that right, Elaine?

MS. COLE: You got the initials right.

MR. ELENGOLD: I got the initials right. That group has changed names at least 20 times since I've started with FDA.

One of the comments we did hear during the grassroots and 406(b) meetings was the need for improved guidance material. Well, the Team Biologics process has led to the formation of more of that. We have issued or are in the final process of issuing compliance programs as products move from CBER lead to ORA lead. We have issued some and will be issuing more inspection guides. We got specific inspection assignments with guidance in them, operational SOPs so that everyone is doing everything the same way across the country. And the Turbo EIR, which is an initiative that ORA started that we have assisted with, which speeds the reporting process so that actions can be taken and files closed faster.

Training activities. This is probably the most

highly trained group of people in the FDA today. We've had six blood banking and plasma courses. We've had two courses on the fractionation industry. We had courses on IVD manufacturing, which is a particular interest to this group. And many of you I know were at the industry workshop that we had in conjunction with the IVD training back over the summer. Allergenic manufacturers training, biotechnology, and we're planning for the summer a vaccine manufacturing training program for the Team Biologics. And we're in the process of holding three or four quality auditing courses.

One of the things that is a parallel issue but related is the GMP Working Group, which was put together under the lead of the Office of Enforcement and the Office of Regulatory Affairs. That group has been trying to address issues that are common across the Centers. And there are members of that group from ORA, CBER and CDER and at a recent meeting we decided to expand that group to include CDRH, so they will be coordinating on these issues, as well.

And so far, some of the issues they've discussed and tried to reach resolution on are viral and activation validation, reprocessing, reworking, blending, validation, particulate matter and inspectional issues.

The implementation schedule for Team Biologics, the first products that went over October 1, '97--plasma

fractionation products. April 1, '98, licensed IVD, and many of you in the room are very familiar with that process. October 1 this year we transferred allergenics and the biotech products. And the last group to go over October 1, '99 are the vaccine products.

And one of the things we hope to accomplish and we have actually in the operations group that oversees the Team Biologics roll-out just about finalized an evaluation plan, is to see how we're meeting our goals. The things we'll be looking for are consistency of agency operations, enhanced coordination, the importance of the program, both to the FDA side and the industry side, industry acceptance and support, which quite frankly has been mixed. Some manufacturers have told me enthusiastically they think this is the greatest things we've ever done. Others have reservations.

Technical expertise of the staff. There's a certification program so that eventually all people participating in this will be certified to a base level. And, of course, our overall goal of consumer protection.

So I just wanted to go over that real fast. Thank you very much. And I honestly do not know who the next speaker is, so I'll ask Dr. Zoon to introduce them. Thank you very much.

DR. ZOON: Thank you, Mark.

Our next session is entitled Perspectives--present

issues from the device industry and the manufacturers' issues. And the first speaker this morning in this program area is Carolyn Jones from HIMA, who will address software.

PERSPECTIVES - PRESENT ISSUES FROM THE DEVICE INDUSTRY, MANUFACTURERS ISSUES

SOFTWARE

MS. JONES: Good morning. First let me let you know that I won't be just addressing software. It's sort of a mixed bag that HIMA represents.

Good morning and I'd like to thank FDA for allowing us this opportunity to present suggestions for improvements to CBER's regulation of medical devices, those processes.

At HIMA I am director of technology and regulation. At present my primary responsibility is in vitro diagnostics and blood bank software. And because we had been hearing so many complaints about CBER activities, we've expanded our activities to include some device groups that aren't represented in those broad categories that I already participate in.

Let me tell you a little bit about HIMA. HIMA is a Washington, D.C.-based trade association and the largest medical technology association in the world. We represent over 800 manufacturers of medical devices, diagnostic products and medical information systems. That's why today

I'm not just speaking with respect to the software manufacturers.

Although the bulk of devices are regulated by FDA's Center for Devices, CBER's regulation of devices is an important issues for many of our members. Increasing delays in product reviews at CBER have increased manufacturers' discontent and frustration with the CBER processes.

Dr. Zoon has already sort of discussed a little bit about FDAMA but just to give you from our perspective what we think FDAMA did, in 1977 the Congress of the United States passed a law designed to remind us that FDA's mission is the provision of safe and effective medical products to the American public.

It was also a reminder that the agency is partnered in this effort with the medical professions and with the producers of medical products.

While in the past, FDA may have thought of its mission as preventing unsafe and ineffective products from reaching the market, Congress has sent us a clear message that such an interpretation is, at best, incomplete. To be considered successful now, the agency must ensure a steady and timely flow of products that are not only safe and effective but that make a significant contribution to the health of the American public.

FDA has responded to this new vision with

enthusiasm and dedication. CBER has canvassed stakeholders and has listened seriously and thoughtfully to their concerns and is moving to address some of those concerns.

HIMA is greatly encouraged by CBER's efforts to gain input from the medical device industry on how it can best improve its regulation of devices. We are glad to see that comments made by the medical device industry at the two national stakeholders meetings hit fertile soil and appreciate that some seeds may have already taken root.

We commend CBER for its recent adoption of previously enacted CDRH inspectional initiatives--the preannounced inspections and annotated FDA 483s. But there is much more to do. We agree with Dr. Zoon that today's meeting to discuss the development of a Device Action Plan is a good first step in that direction.

Any new project should begin with an evaluation and that evaluation should take into consideration the tools that you already have at hand and those needed to perform the task. To develop a 1999 Device Action Plan, a good starting point for CBER is to first evaluate all of its current processes to determine what things add no or little value to the process. Stop all functions with little or no pay-off. Expand those that work and look for new approaches to enhance the process. This kind of introspection, while difficult, will result in a more efficient organization that

meets all of its laudable goals outlined in the mission and vision statement.

Some specific suggestions that we have--one of the things I think that has bothered the medical device industry is we sort of looked, reviewed carefully the mission and vision statement. We saw that one of the things that was missing was any specific reference to medical devices in the mission statement. And we viewed that in some ways as a sort of example of one of the problems we've seen with CBER.

Some device manufacturers believe that CBER has little interest in reviewing products that don't generate user fees. We believe that CBER's disinterest is evidenced by a noticeable absence from CBER's current mission statement of specific reference to medical devices. That may not be true but that is the perception.

Including medical devices in the mission statement would go a long way to correcting the perception that CBER has little interest in medical devices because they do not generate user fees.

CBER should clearly outline its medical device-related FDA Modernization Act implementation programs.

For some time, the medical device industry has been both confused and frustrated by the seeming lack of activity within CBER regarding implementation of the FDA

Modernization Act. While CDRH has had the bulk of the work in developing and implementing programs and policies for devices, CBER has been slow to develop its own policies or to indicate which CDRH policies it will adopt.

CBER should adopt the CDRH initiatives that are well suited for its programs, use some of the tools implemented by CDRH, such as the 510(k) paradigm, modular PMAs and product development protocols. These could greatly improve CBER's product review processes.

Harmonize the review processes. CBER's review processes with regard to instrumentation and software could be reharmonized with CDRH's review processes so that instrumentation and software that can be used for both blood screening or diagnosis will not require dual review.

The device industry recognizes that CBER's paramount concern is the safety of the nation's blood supply. Where necessary to address specific CBER concerns, add requirements in a consolidated guidance document. Harmonizing the device reviews would streamline this process and facilitate getting new technologies to market.

So we're not saying that you have to adopt CDRH's software policies or instrumentation policies in total but we're saying that the bulk of that information is useful to the CBER processes. And where it doesn't fit, where it's not a nice, neat fit, you can put specific guidance or

specific requirements in place that would make the areas where you need to protect the blood supply.

Work with industry to develop templates and guidance documents to make each type of submission--the BLA, the 510(k) and the PMA--and review processes simpler.

The medical device industry has not been given the opportunity for meaningful participation in CBER's guidance development process. CDRH has already recognized that much can be gained from earlier interaction between the agency and industry during the guidance development process. In fact, industry has developed the initial drafts for a number of guidance documents at CDRH. We believe that CBER guidances could well benefit from this type of collaborative effort.

One of the other things is that manufacturers have complained that sometimes it seems like their submissions are sort of lost in a black hole and they don't know where they are. I think it would be helpful for CBER to publish flow charts of internal processes for all submissions so that the process is transparent. Indicate who's accountable for the process at critical points.

Publish the flow charts of internal processes for the well-defined points so that firms can, at key committee review points, get feedback and talk to FDA about concerns with the submissions. The feedback could be done via

teleconference and cover questions that might require additional investigational data. It would help both industry and FDA reduce the cycle time for product development and review.

It should also attempt to improve the access to scientific and technical expertise. One of the issues that FDA as a whole has to come to grips with is that it cannot always keep up with the advances in the technologies that it regulates. CBER is no exception. Many of the delays in certain product areas can be directly linked to a lack of understanding of the technologies.

It is in CBER's and industry's best interest, as well as the public's, to make sure reviewers can keep current. CBER should make more use of scientific workshops to gain a broader perspective on scientific and technical issues.

Workshops permit an open dialogue and exchange of ideas, which is precluded by the advisory committee structure. Bringing products to advisory committees doesn't allow that true exchange.

CBER has already conducted a workshop addressing implementation of nucleic acid testing for HIV for blood screening and another for nucleic acid testing for hepatitis and other viruses. We hope that this will continue and expand into other areas, as well.

We realize that workshops can be resource-intensive, and Mark gave a good presentation of the what the status of CBER resources is at this time. FDA should consider allowing industry or professional associations to cosponsor or even sponsor workshops, where possible.

The CDRH vendor day program should be expanded to include products regulated by CBER. In addition, CBER reviewers should be allowed to make site visits to device companies to gain a better understanding of the products they regulate.

CBER should consider reallocating some of its resources to clear up the backlog of device reviews, much like its sister Center, CDRH. This means temporarily placing research projects on hold to help accelerate the process of getting new devices to market. This would be an effective and efficient way of reducing the current product review backlog.

I recognize that Mark has indicated that the resources in the research area have already been significantly reduced and I don't want to leave you with the impression that we think those research activities should be discontinued. But in times when there are significant backlogs and significant problems within an organization, you have to take a step back and reprioritize.

And at this point, with the significant backlog, it may be a good idea to look at other resources within CBER that may be doing things that possibly don't add a whole lot of value at this time but may add value in the future. Don't discontinue them but put them on hold for a little bit.

Also one of the things that device manufacturers, you'll probably hear throughout the day, is the necessary to adopt CDRH device initiatives such as warning letter pilot program and some of the FDAMA initiatives. You'll probably hear that over and over again.

But with respect to the warning letter pilot program, we suggest that CBER adopt the warning letter program. We realize that this will require slight and possibly painful attitude adjustment. The current program, with its focus on metrics rather than correction, adds little to CBER's ultimate goal of a safe blood supply.

The warning letter pilot program has the advantage of allowing the company to make a commitment to correct any deviation without the need for a warning letter. If the commitment is not met, the option of a warning letter is still available. The program has proven successful at CDRH and I think it may add some benefit to the CBER program, as well.

While most of our concerns right now are directed

at the product review, some of our companies have expressed concern with the Team Biologics approach and I did have some comments in my presentation with respect to that. But I think they should be held for later discussions with the agency because I think there may be some misconception on the manufacturers' part as to the focus and direction of some of the Team Biologics activities, so I will put those on hold.

But in closing, HIMA thanks FDA for the opportunity to provide suggestions. We hope that today's meeting demonstrates a true willingness to work to improve CBER processes so that the mission and vision that CBER has outlined can be met.

We look forward to working with CBER as a partner in this effort to continue to improve the review and inspection programs. Thank you for the opportunity to present these comments. We hope that this again will be the first of many efforts to improve the processes at CBER.

DR. ZOON: I've just been informed that at the break we'll be getting some more chairs, so that should give you some more comfortable facilities.

I want to thank Carolyn very much. I look forward to working with her and her colleagues and I think many of the points, again Carolyn you've made, reiterate what we heard in the 406(b) meeting and I think that's important

that we're getting at least a consistent message on some of the issues that people believe are important, so thank you very much.

Our next speaker this morning is Dr. Steven Binion from Baxter Healthcare.

EQUIPMENT/SUPPLIES

DR. BINION: Good morning.

Just a couple of background comments about the Fenwal Division of Baxter Healthcare, which I represent. Fenwal is a manufacturer of drug and device products which are used in the collection, processing, storage and administration of blood components. And in the U.S., all of Fenwal's products are regulated through CBER's Office of Blood Research and Review.

On behalf of the Fenwal Division, I want to thank CBER for organizing this workshop and for providing an opportunity for a variety of individuals to be heard on the topic of CBER's regulation of blood technology devices.

While sometimes referred to as niche products, blood technology devices represent a significant industry in the U.S. and abroad. More importantly, these products play a key role in maintaining and improving both the availability and safety of the supply of blood components for transfusion and blood components for further manufacture.

It's very appropriate and timely for the agency to seek feedback concerning the regulation of these devices and Baxter applauds the agency's initiative in this area.

What I hope to accomplish today is to provide a brief overview and I will try and be brief, since I realize I'm the only thing between you and the break. But I'd like to address several aspects of CBER's device regulatory process from my perspective in industry.

I'm going to focus on three key elements in the regulatory scheme--the people involved in device regulation, the products that are regulated and then finally, the process which CBER and device manufacturers use to bring these products to market.

Given the limitations of time and also my individual perspective, it's unlikely that I will address all the points that are relevant to today's discussion. However, I hope that I can provide some useful commentary and perhaps one or two recommendations which may be of interest with regard to CBER's Device Action Plan.

In terms of the people at CBER, it's clear that the reviewers and other staff involved in blood technology device regulation face a daunting and perhaps unenviable challenge. In order to be effective in their role, CBER reviewers must combine expertise in blood banking, biologics and medical device regulation, while trying at all times to

process their workload in a timely manner.

This is certainly no small task, especially in light of the budgetary and staffing constraints, as previously addressed by Mark.

Those of us in industry also face constant pressure, as well as internal resource constraints, also associated with the product approval process. And we certainly have a very close-up view of the agency's issues and efforts in this area.

In terms of recommendations, the first one that I would offer simply recognizes the fact that at present, devices are not user fee products. With this in mind, it's important that CBER explore and look to implement resourcing alternatives which may be available to assist in the review and approval of blood technology devices.

At a minimum, this type of internal review is likely to identify strengths and weaknesses in current CBER operations.

A second recommendation is that CBER work with industry to create opportunities, and here I'd like to stress additional opportunities for reviewers and other staff to meet with manufacturers in order to increase the reviewers' familiarity with the design and use of the products which they regulate and also to provide additional opportunities for CBER staff to communicate requirements and

expectations to the industry.

Fenwal has participated in several device demonstrations in FDA's Chicago District Office and the program has been beneficial to both Baxter and, based on the feedback, to the agency.

This next comment reflects my experience in dealing with CBER on a variety of device issues during the past five years. As CBER looks to make the best possible use of its people, I would point out that in many instances it is critical for a manufacturer to be abe to interact directly with the reviewer on a technical issue. This type of access benefits both the manufacturer and CBER in the overall process.

In addition, as CBER looks to improve the device regulatory process, the value that industry places on timely communication of issues and progress through the review process cannot be overemphasized.

Accessibility and timely communication are two people skills that are critical in this area and will be critical to CBER's success in the future.

Finally, it is worth noting that we in industry share a number of goals in common with the people of CBER. In particular, we, too, are committed to providing safe and effective devices for use in the nation's blood-banking industry.

Turning now to the issue of the blood technology devices which CBER currently regulates, Fenwal supports the concept of CBER maintaining responsibility for medical devices which are used for the collection, processing, storage and administration of blood components for transfusion. Given CBER's overall responsibility for the blood supply of the nation, it is appropriate that these devices are also regulated by CBER.

Currently the majority of these devices are regulated through the 510(k) process, which is used by CBER as an adequate regulatory mechanism to address relatively complex devices, such as automated blood cell separators and the aphoresis kits which are used with these instruments.

One suggestion for improving the regulatory process for blood technology products is that CBER investigate the possibility of reclassifying blood pack units which contain anti-coagulants or other solutions, as 510(k) devices. The device components of these products, which are currently regulated as drugs, could just as effectively be regulated as 510(k) devices while the anti-coagulant and other solutions remain covered by the corresponding new drug application.

This change would potential streamline the regulatory process for manufacturers and the agency. It might also help address some of the concerns around product

approval times and CBER resourcing.

And I would point out here that in the instance of Fenwal's drug devices as used for blood component processing, these NDA products are also, by law, not subject to user fee payment.

Another area of blood technology device regulation which CBER must continue to address is the need for finalization of the regulatory framework for devices which are used for the collection and processing of minimally manipulated stem cell products. Over the past few years, several draft guidances have been issued for comment, but the regulatory status of these products is not yet fully defined.

The third recommendation related to 510(k) devices is that CBER identify for manufacturers those 510(k)-related process improvements which can be applied to blood technology devices and work with manufacturers to identify specific circumstances in which blood technology device changes require no 510(k) or only an abbreviated 510(k) submission.

Looking next at PMA devices, this product category obviously contains those devices which are associated with the highest risk and/or regulatory complexity. While generally asking that CBER examine recent PMA process improvements as adopted by CDRH, one very specific

recommendation is that CBER designate a category of blood technology devices which qualify for expedited review by the Center for Biologics.

Two key elements of this proposal might include the requirement that such products represent an important new technology or technologies and that these products also contribute significantly to an improvement in the safety of existing blood products.

This change would be an important step forward in addressing industry's concern over the availability of new technologies and in demonstrating CBER's commitment to blood technology devices.

Adoption of a modular approach to PMA submissions and reviews would also help streamline the review and approval process. And again there's a model within recent process changes adopted by CDRH that could be followed here.

Similarly, CBER adoption of the so-called realtime review for minor PMA product changes could be specifically adapted to blood technology devices and has the potential again to improve the product review process from the standpoint of both industry and the agency.

In closing, I'd like to offer just a few additional comments concerning the overall regulatory process. As I mentioned earlier, manufacturers of blood technology devices share a number of goals in common with

CBER. And as we move forward in this activity, both manufacturers and CBER need to share a commitment to improving in the following areas. And I think clearly I'm talking about improvements on the part of both parties in this area.

Number one, to focus on this sector of medical devices. Clearly these products are recognized by manufacturers, the blood-banking community and the agency as being important components of the preparation of the nation's blood supply.

Both industry and CBER need to focus on maintaining and improving access to one another throughout all phases of the regulatory process.

And finally, we have to agree to make a commitment to the best possible interaction between CBER, manufacturers and the customers who use these products and who are, in turn, regulated by CBER. Thank you.

DR. ZOON: Thank you, Steve.

We'll now take a 15-minute break. We're on schedule so we'll resume at 10:15. Thank you.

[Recedes.]

MS. EBERHART: Our next speaker is Dr. Paul McCurdy. He's from the Heart, Blood and Lung Institute. He's a consultant.

DR. McCURDY: Actually it's the Heart, Lung and Blood Institute. Lung got there before blood did, for whatever reason--a better lobby, I think.

I was, until last January, the director of the blood resources program in the Blood Division of the Heart, Lung and Blood Institute and as was mentioned, I'm now a consultant to the director in the blood resources area.

I've had a moderate amount of experience with the FDA and its predecessors. I was involved with regulatory agencies from approximately 1956 to about 1986 in one way or another and since I became a member of the Institute, we worked closely with the FDA on a number of the research projects that the Blood Division and the Blood Resources Transfusion Medicine Section sponsored.

I watched the initial incarnation of what is now the Blood Product Advisory Committee, maybe BPAC 1, which in the '70s reviewed all of the blood products and made recommendations for specifications and so forth. Unfortunately, many of those disappeared without a regulatory trace in the next five or eight years. A lot of it was caused by the AIDS epidemic.

The NHLBI, the Heart, Lung and Blood Institute, is the lead agency in the Public Health Service and at NIH for research in transfusion medicine and blood safety. When we're dealing with the possibility of products that may be

regulated, I've looked upon our role, at least in part, to provide the research to help provide a scientific basis for regulation. And in that, we have attempted to work closely with the FDA.

I'll mention a few examples and, in the process, note some of the good things that we've been able to accomplish and perhaps a couple of problems.

I've approached our work with things that are usable with the idea that they should be able to be used and there shouldn't be any regulatory impediments to getting them used. And in that line we've supported basic studies. Sometimes they've been followed on with corporate support for application. An example are some studies the Institute supported in the inactivation of viruses, first in plasma and more recently in cellular components that are beginning to move forward.

We also support clinical studies when corporate support is unlikely, at least at the beginning, and several of the examples I'll mention lie in that area.

We've been supporting now for about five years, I think, a trial to determine whether T-cell depletion of a bone marrow transplant before the transplantation would prevent graft versus host disease, improve the overall survival of the patients who get bone marrow transplants without penalties of graft failure and some other side

effects of T-cell depletion.

There has been now for 10 or 15 years a debate in the bone marrow transplant community as to whether graft versus host disease in the unrelated donor setting in particular is so bad and so difficult to manage that you need something like T-cell depletion.

We have two devices that are things that would probably be regarded as devices that are being used in this trial. One of them is elutriation to remove virtually all of the lymphocytes and to concentrate the CD-34 positive cells, and we're using another device, an antibody device, to further purify CD-34 cells from the nonusable fractions and add them back in order to get a fairly large dose of CD-34 cells. These are both devices that ultimately will need to be approved for use if they turn out to be satisfactory.

The other one is an antibody that removes T-cells by agglutinating them and then differentially centrifuging them out. So-called T10B9 antibody.

From the very beginning of this trial, we recognized that for the results of the trial to be widely applied if they're positive, there would need to be approval at several levels at least in the FDA for that. We worked with our own biostatistical group in designing the RFP. We also discussed it with members of the FDA as we were

developing our request for proposals.

There was a problem, however, that developed in this and it's a recommendation that I might make for the FDA to consider. That is decisions made by one individual early in our designing of the trial turned out, when that individual left the project, not to be supported by the next person that took over the management of the trial from the FDA's standpoint.

This was not necessarily a bad decision, to change that, but it reflected some lack of continuity and a potential problem there, and I think cost us probably somewhere between six months and a year in getting the trial started.

Another area that we're now supporting a clinical trial is a simple little efficacy trial without any comparison. The first, the T-cell trial, is a randomized multi-centered trial.

The other trial is an attempt to determine whether cord blood stem cells, which have received a fair amount of publicity, particularly in the last week as a result of publication of the largest series from the pioneer in this area, Dr. Pablo Rubenstein. It received some press, I understand it--there was a large article in the New York Times.

We also worked very closely with the FDA and with

our own biostatistical group in designing the RFP, determining how many cases we needed, what our goals were and so forth. In this situation it's not absolutely clear how cord units are going to be regulated. It's been my opinion that they probably should be licensed as a biologic but there are other possibilities that will protect the public.

This has generally gone very smoothly. We've appreciated the assistance that we've had from the FDA in helping us get this trial under way and following its progress.

A third example, the Institute is now about three years, I believe, into the development or sponsoring the development of a genomic amplification test or nucleotide amplification test for blood screening, aimed initially at HIV and hepatitis C virus.

This turned out to be a completely new approach to the screening of blood, with which none of us had a great deal of experience. There was no precedent as to how many cases or what the end points should be.

We worked closely with the FDA staff on this but most importantly, we went to our own biostatistical group and told them what kind of confidence limits we would like to have, what our approach was going to be, what the results were, and asked them to tell us how many individuals needed

to be tested in the clinical studies. This was very important.

There was, however, somewhat of a problem and that is that since this is new technology but also because there's been a progressively increasing scrutinizing of computer software and validation at a number of different steps in this process, this is partly, not totally but partly responsible for somewhat of a cost overrun and a delay in that we're a bit behind schedule.

I don't think that there's much of anything that I can recommend to the FDA that they do about this. This is the state of the art. This is a new area and it needs to do that. It needs to be carefully looked at in view of additional information.

There is one question that I did not take the opportunity to ask during the intermission but we've had some interest from the AIDS community that our test for AIDS, our nucleic acid amplification test for HIV virus, would be useful in clinically diagnosing cases very early in the process, particularly people who've had point exposures of one sort or another. And there's interest in our providing the test for that purpose.

I guess my question is would it be necessary for this if it were to become a diagnostic test, as well as a blood screening test, would it be necessary to get a

separate submission to CDRH and a separate review and a separate study? It would seem to me that something that's adequate for screening blood ought to be adequate for diagnosis--probably but not necessarily adequate for quantitation but adequate for diagnosis.

When we've had investigators come to us with clinical trials that they're proposing or when we put out an RFP for some clinical trials if they involve the FDA, we make every effort to insist that the investigators consult with the FDA very early in planning so that if the results of the trials turn out to be positive, there won't be any particular glitch in getting the approvals that are necessary.

I've mentioned a couple of problems. There's a third problem, which I observed initially back in the late '70s but in checking the devices that have been approved in the last year by CBER it's cropped up again. That is the licensing or the approval of a device to provide a biologic product which itself is not yet licensed.

The example from the late '70s, there were a number of phoresis machines that were available and approved for sale, were on the market providing platelet phoresis. It wasn't until the early '80s that platelet phoresis products were licensed and shippable across state lines.

At that time I happened to be the director of the

large regional blood program in the District of Columbia. I could spit across a state line in either direction. You also needed a license to ship it out the front door because that's the way the original law was written. You could ship a product from one end of Texas to another, as one of my friends said, to save a life or the reverse, but I couldn't send it out the door.

It generally removes the incentive for people to gather the data necessary for licensure if this happens.

I noticed that last summer there was approved an umbilical cord blood collection device. There's a lot of interest in cord blood. There are a lot of people that are involved in cord blood transplantation, cord blood collection, but there are a lot of questions that we need to answer before it's appropriate to bring them into the routine therapeutic armamentarium. Thank you.

MS. EBERHART: Thank you, Dr. McCurdy.

The next speaker is from ThermoGenesis and it's Mr. Phil Coelho.

SMALL COMPANY PERSPECTIVE

MR. COELHO: First of all, thank you for the invitation for speaking here today.

Just to give you a perspective on my comments, ThermoGenesis, for those of you who don't know, is a small medical device manufacturer based in California. We have

previously developed and marketed ultra-rapid plasma freezers and plasma plasmathars which we sell to blood banks, either in the hospital or blood banks.

We have recently been working on the development of a little more complicated devices. Those were Class 1 devices so the new ones are Class 2 devices. They're different for us as a company in the sense that they are not only a device, which is the machine in this case, the thermodynamic machine, but also single use sterile disposables, which actually contact the blood. So that's a kind of upgrading of the complexity before our company and, of course, our regulatory submissions bear the burden of that.

Our recent involvement with these new products have exposed weaknesses in our own company and in the course of the regulatory efforts we have been making, they have also aroused in us some suggestions about how the process might be approved.

In listening to the previous speakers, I don't think there's anything I'm going to say here that hasn't previously been said and said better, but I'll kind of take a whack at it.

If I were to summarize it, as I understand it, it's kind of borrowing from the Gatorade commercial about Michael Jordan--you know, "Be like Mike." What I hear

people saying is "Be like CDRH." I'm embarrassed to say I haven't read the new CDRH regulations. All of ours have gone to CBER.

First of all, it's fair to say that in the course of our involvement with CBER, we are aware of the rather severe dilemma. The cutbacks have been onerous in staff. There's a public obsession with safety. The press is second-guessing every decision you make. If you screw up, they're all over you.

Companies are clamoring for approval and the public basically wants their life extended so it averages 200 years, so every new product, every new device, every new drug is going to have them get that way and you're merely the enemy if you stop them from coming to market in a hurry.

One thing that is also clear to me in the course of it is that like with many companies who have cutbacks, everyone that I've met at CBER is working real hard. You're basically expected to do what you did before but with 20 or 30 percent fewer people.

We're a company that's gone through a 30 percent cutback ourselves, so I have some sense of that. And you should believe that people in industry, including the Mobil and Exxon employees here, are soon going to find out what it's like to do more with less. It is something we can empathize with.

I've kind of divided this up. There is some advice which we have learned over the last couple of years that I wish we had understood better in making these more recent submissions.

One of the things is, strangely enough--so this is kind of voiced in the way of advice that CBER might give small companies. Although you can't really demand this, but mainly hire a consulting firm. There are people out there, some of them former FDA employees, who can give you advice that is absolutely indispensable to doing this thing correctly. We've used Hogan & Hartson and we've used Emily Rossiter, et cetera. Every contact we've had with them have saved us money.

Another is try to have premeetings before you present, so that you're real clear on what the CBER is likely to want with this particular device.

Another one is when you write your submission, one of the things I would recommend and that we will do in the future is to write it in such a fashion that it's clear to an uninvolved nontechnical person. What you have is if you have devices that unusual in any respect, the people who are writing it are so imbedded into the device, they write it in such a fashion that it may be clear to them but it's not necessarily clear to someone else.

So I think we will literally have people in our

company that are nontechnical and not involved read every single submission we make in the future in detail. And if they ask a question, it's likely to be asked by someone at CBER, the same sort of question. So we need to do a better job of anticipating that because you can't expect them--anyone else outside--to be as imbued in the product as you are.

Also if the device is unusual in any fashion, and our two new devices are quite unusual in the sense that they're a single platform that replaces a variety of other devices, then I suggest that you press for a meeting where you can demonstrate it. That's kind of a back-up of writing the explanation in sufficient detail that nontechnical people can understand it.

There's nothing like a show and tell. We've used it in the past. I think it was helpful for us.

The other is press for interactive meetings with agendas in advance. There have been in the past times where everything must be in writing and things that could so easily be cleared up with a little interactive communication, all of a sudden you're back in the queue, another 90 or 120 days is going on and you're frustrated and waiting. I think this has got to be as frustrating for the CBER people as it is for us.

And the most important meetings we've had have

been interactive ones, where you get questions asked right there and you can answer them right there and it saves time for both CBER and ourselves.

We made another mistake. We submitted data on a study that had sampling errors in it. And as a result of that, we explained them and went on. We were rushed, wanted to get the data back in. One suggestion I would make is that if you have any of those kinds of errors that you simply start all over on a clean piece of paper because anything that you submit that is confusing in that fashion, your explanation's only going to go so far, so it's better, cheaper, faster ultimately to start all over, spend the money, redo everything, do it correctly this time and that will be good for the company.

These are kind of suggestions that to the extent that CBER can advise small companies, I think it's a good thing to do.

In regard to CBER themselves, the corollary of this is to grant interactive meetings. It's got to be more efficient for them, as well.

Secondly, if there has to be follow-up meetings, we would appreciate having our specialists deal with the CBER specialists. So if this is a software issue, it really doesn't need to tie up all the other CBER people in a meeting on a software issue. If our software specialists

can talk to their software specialists, a lot of this can move more expeditiously.

We've had several meetings where there's been a whole group of CBER people and a whole group of our people, but the real communication was in a very select thing. So there are a lot of people tied up in the meeting who didn't really have to be in that meeting.

Also, if a company presses and you agree, to have a demonstration. It's real important to get the people from CBER who really can gather in the salient information about the demonstration there at that meeting. It's frustrating to have a meeting with a demonstration and find out a key person wasn't there, so basically all of this was for nothing.

Also, this has, I'm sure, been suggested by other people but there may be some Class 1 devices--I understand some of these now are going out of your review period, but the degree to which you can pass on and not give the same attention to simpler devices in order to devote more time to the more complicated Class 2 and Class 3 devices, that would be a suggestion that I would make.

I think a final note is from a small company perspective, borrowing from Fitzgerald's remark about the difference between rich people and poor people--the rich people have more money--small companies are fragile, but

sometimes we also have good products that can be of benefit to patients. An extended delay for a company like Baxter may mean a little less revenues in that area. An extended delay for a small company can be crucifying.

So it doesn't mean that the standards necessarily--they shouldn't be reduced, but just be aware of the consequences sometimes for small companies of extended delays. They are significant.

That's it. Thank you very much for your attention.

MS. EBERHART: Thank you, Mr. Coelho.

The next speaker is Bernard Branson from the Centers for Disease Control.

CENTERS FOR DISEASE CONTROL

DR. BRANSON: Good morning. My name is Bernard Branson from the National Center for HIV, STD and TB prevention at the Centers for Disease Control and Prevention. CDC appreciates this opportunity to offer comments to CBER on the development of a Device Action Plan and on their efforts to improve the regulation of medical devices.

Most of the medical device applications reviewed by CBER are related to issues of blood safety under FDA's mandate for the protection of public health. CDC's interest, in addition, relates to FDA's broadened public

health mission, not only the protection of public health, ensuring safety and efficacy of medical devices, but also the promotion of public health through ensuring the timely availability of devices important for unmet medical and public health needs.

Considerations of safety and efficacy must take into account not only the performance characteristics intrinsic to the diagnostic devices when they're used for blood screening but also the public health implications and benefits and risks when these devices are used for screening in other settings.

The requirements for approval of devices intended for donor screening are explicitly designed to protect the safety of the blood supply. However, many transfusion-transmitted diseases can also be transmitted through other mechanisms, such as sexual contact, needle-sharing by injection drug users and during pregnancy from an infected mother to an unborn child.

Because of these circumstances, regulatory criteria sometimes lead to a paradox. The requirements necessary to ensure efficacy of devices for donor screening may impede or delay the availability of devices intended for other screening situations with substantial public health benefit.

I'd like to illustrate the situation with the

example of HIV rapid tests. The virtual elimination of transfusion-acquired HIV is a testament to the success of CBER's scientific, regulatory and review process. However, both the technology for HIV diagnostics and the landscape for HIV prevention continue to evolve.

In the United States, tests designed for donor screening led to the predominance of complex, batch-oriented immunoassays. From experience, we've learned that this time-consuming technology complicates HIV screening in other venues because many persons who are tested never learn their HIV test results. Of the 37,000 persons who tested positive for HIV at publicly funded programs in 1995, more than 9,200, 25 percent, never returned to learn their test results.

Rapid test could practically eliminate this problem. Based on studies using rapid test, CDC estimates that 8,200 more infected persons would have learned of their HIV infection if rapid tests were used in 1995.

The need for immediate HIV test results for making decisions about treatment has made the demand for rapid HIV tests even more urgent. A recent study from New York demonstrates reductions in the rates of perinatal HIV transmission from women who had not been tested during pregnancy when antiviral therapy was begun intrapartum or given to the infant within the first 48 hours of life.

Routine, voluntary HIV testing of women in labor who have not been tested is likely now to become the standard of care and for this we need accurate rapid tests as soon as reasonably possible.

Meeting the public health needs for timely HIV diagnosis requires the availability of additional HIV rapid tests. Using the single currently-approved rapid test alone poses problems because many false positive results will occur when a single screening test is used. When two or more sensitive and specific rapid tests are approved, the Public Health Service can develop a diagnostic algorithm based on combinations of rapid tests, similar to that recommended for several years by the World Health Organization. And use of a second or third rapid test to corroborate the results of a positive screening test significantly improves the predictive value of a positive tests and greatly improves the value of rapid testing for making treatment decisions.

Although many rapid tests for HIV have been developed by U.S. manufacturers and are widely available internationally, paradoxically, few have been submitted for FDA approval and only one is commercially available in the United States. The reasons these tests are unavailable is multiple. Among the reasons cited to us by manufacturers are the complex requirements, cost and time associated with

FDA approval. The requirement for group O sensitivity represents one example.

Based on the recommendation of the Blood Products Advisory Committee, CBER requires that all new HIV tests detect antibody to group O virus. Even though many HIV tests currently available in the United States do not detect group O, any rapid test submitted for approval must now meet this requirement. This is likely to delay the availability of rapid tests, which are intended to be used in settings other than donor screening.

CDC agrees that it's desirable for every diagnostic test to be able to detect subtypes such as group O and other variants as they occur. But these are very uncommon viruses in this country. Although it is important to screen donors for these rare viruses in order to protect the blood supply, we must also consider our responsibility to facilitate diagnosis for many HIV-infected persons who could benefit from treatment.

CDC currently estimates that there are approximately 250,000 persons who don't know of their HIV infection. Data show that many of these persons currently pass through emergency rooms and out-patient clinics without learning their HIV status.

Rapid tests could make it feasible to offer testing in these and many other settings where it's

currently impractical, and we have already documented that many more persons receive their test results when rapid tests are used. Delaying the availability of rapid tests until they demonstrate sensitivity for rare HIV strains thus hampers our ability to detect a large number of persons infected with common group M strains.

Because no screening test is perfectly sensitive, a small percentage of false negative tests will occur. Even using tests that lack sensitivity for group O, however, more false negative results will occur among persons infected with group M than with group O viruses simply because group M infection is so much more common than group O infection in the United States.

HIV tests for diagnostic use only constitute a separate category from HIV tests intended for screening blood products, for which different criteria for approval are warranted. In establishing the criteria for diagnostic use only tests, CBER may also want to consider the appropriate mechanism for evaluating the potential risks and benefits for public health unrelated to blood safety.

At CDC recently, we have had to bring together advisory committees from two different centers to discuss the issue of transmission of HIV from health care workers to patients because neither committee alone had adequate expertise to provide our agency with the best direction.

CBER may want to consider whether the Blood Products Advisory Committee, establishing for developing criteria for blood safety, represents the optimal forum for evaluating medical devices intended only for diagnostic use or alternatively, whether it should be supplemented with more experts in clinical medicine and in public health.

Two other points that might improve the timely availability of medical devices echo points that were raised during the previous stakeholders meetings. The first relates to the timetable for reviews for in vitro diagnostic submissions. The large number of applications and the resource limitations within CBER may sometimes cause these reviews to be delayed or to receive lower priority, resulting in a lengthy review process. It may be useful to specify criteria and procedures for expedited review of medical device applications submitted to CBER, similar to the revised policy issued by CDRH in March of this year, so that devices which address specific unmet needs receive priority attention.

The second point involves the transparency of CBER procedures. We would like to acknowledge the substantial efforts CBER has made, especially in making information available through its web site. However, we have noted that it is sometimes difficult to identify a comprehensive summary of the performance requirements expected for

diagnostic devices.

For example, in recent years a number of specific requirements for the clinical evaluation of in vitro tests for HIV have been expanded. However, the draft of points to consider, which outlines required aspects of clinical trials for HIV testing, has not been revised since 1989 and does not include several of the current requirements.

We would recommend that summary documents, such as draft points to consider, be updated as additional requirements are developed in order to disseminate this information and to facilitate communication between CBER and individuals interested in making applications to the FDA.

Thank you once again for the opportunity to provide remarks at this meeting.

MS. EBERHART: Thank you, Dr. Branson.

The next speaker is Kay Gregory from the American Association of Blood Banks

BLOOD INDUSTRY

MS. GREGORY: Good morning. The American Association of Blood Banks is pleased to have this opportunity to comment on the development of a CBER Device Action Plan.

The AABB is a professional association for approximately 2,200 institutions engaged in the collection and transfusion of blood and blood products, including all

American Red Cross blood service regions, independent community blood centers, hospital-based blood banks and transfusion services. And we're also the professional organization for more than 8,500 individuals engaged in all aspects of blood collection, storage, processing and transfusion.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. The AABB's highest priority is to maintain and enhance the safety of the nation's blood supply.

The AABB's primary concern is that CBER develop a plan which results in the quickest possible review and clearance process for medical device 510(k) notifications. The delay in getting new technology on the market should be as minimal as you can make it. CBER should streamline the 510(k) notification and review processes while conserving industry and agency resources and still protecting the public health.

One area that is of particular concern is the extensive delays reported by our members in obtaining clearance for blood-banking computer systems. A second area of concern is the overlap between review for the device and licensure of the product manufactured using that device.

We do have some specific recommendations we

believe would contribute to the streamlining process. First, I'm not going to be saying anything that you haven't already heard, but first we would like to see you harmonize CBER and CDRH requirements. CDRH has issued many guidances pertaining to device submissions but it's not clear whether these guidance documents also applied to the CBER review process.

CBER should make it clear when they concur with the CDRH guidance. For example, will CBER adopt the innovative approaches such as special 510(k) device modification and abbreviated 510(k) submissions? What are the criteria for removals and corrections with regard to medical devices?

If CBER does have different expectations, and you might, then we would like to have additional guidance issued.

Reviewers must also have the technical expertise to review submissions. If adequate numbers of qualified reviewers do not exist within CBER, this further delays approval. Again our members cite this as a concern with particular reference to blood bank software and believe that CBER could benefit from the technical expertise in reviewing software that exists in CDRH.

Of course, one way to harmonize the requirements and provide consistent expertise would be for a single

center to be responsible for all medical device evaluation and review of 510(k) and PMA supplements. For manufacturers, this would have the added advantage of eliminating the extra burden of monitoring guidances and understanding the expectations of two different centers.

However, we're not really recommending that. There are other ways to accomplish this. CBER could accomplish this goal by adopting the CDRH model for review and by providing adequate numbers of qualified reviewers and explicit and timely guidance.

We also support the CDRH concept of utilizing a review system based on the complexity and the level of risk posed by the medical device and urge CBER to adopt this same approach. This approach is consistent with the current approach in biologics, in which risk is a criteria in determining how to report changes to CBER, for example.

Next we'd like to see you develop guidance documents. We suggest that some of the confusion is due to the lack of guidance as to when submission is necessary, as well as what is to be submitted. Too often it seems that requirements are not clearly delineated and manufacturers become aware of them only when they're notified of difficulties in the submission.

It also appears that CBER waits until after a number of submissions have been received before deciding

what is really required in a submission.

We encourage CBER to follow the CDRH lead in providing clear guidance. As stated in the March 20, 1998 publication from CDRH entitled "The New 510(k) Paradigm," over the past few years FDA has been placing greater emphasis on the development of guidance documents to communicate regulatory and scientific expectations to industry. With the advent of good guidance practices, device-specific guidance documents are developed with public participation.

The main focus of these guidance documents is the identification of the information recognized as appropriate for marketing authorization.

AABB agrees that a 510(k) submission that conforms with an FDA guidance document should be easier to prepare and review, thus resulting in a more expeditious evaluation and clearance of the 510(k). This would be true not only for the traditional submission but also for alternative options, such as a special 510(k) device modification and abbreviated 510(k)s.

We further emphasize the importance of public participation in the development of such guidance. CBER must be willing to consider manufacturers' comments and, where appropriate, incorporate their suggestions into guidance.

Clarity is especially needed in the area of blood bank computer requirements. Despite repeated input from the blood-banking community and software manufacturers, the current document being used by CBER is still just a draft document, draft reviewer guidance for premarket notification submission for blood established by computer software, which was issued in April of 1996.

Currently our members also report that the review process is very reviewer-dependent. Clear guidance documents should also eliminate ad hoc approaches and inconsistency between reviewers, since expectations will be known not only to the device manufacturer but also to FDA personnel.

Finally, we wed like to minimize review overlap. CBER is perhaps unique in that it is responsible for review of submission concerning the medical device and, at the same time, CBER also regulates the users of the device. Thus within CBER we have two separate sets of licensure-type reviews: the 510(k) for the device itself and the BLA license review as users of the device.

Blood banks are subject to two delays in getting new and improved product to our patients--first in the time it takes to get the device approval, then in the time it takes to obtain product approval. This is especially apparent for aphoresis equipment.

The Coalition for Regulatory Reform has suggested to FDA on numerous occasions that once a device has been cleared, blood banks, as users of the device, should be free to utilize that device immediately to manufacture products and should not have to wait for additional CBER licensing approval.

Particularly when the same agency is reviewing the 510(k) notification, it should be possible to minimize the time required to approve the use of the device by blood banks. And it certainly should not require a licensing supplement submission for each location which will be manufacturing the product using that same device.

This system creates unnecessary delay in getting new technology to the market, technology which is specifically designed to improve the quality of the nation's blood supply.

In closing, AABB would like to thank CBER for holding this public workshop. We believe it demonstrates a number openness and willingness to respond to industry concerns. Unfortunately, this meeting had a short lead time in which to develop these comments and we were not able to provide in-depth ideas.

We look forward to working with the agency on this important effort and anticipate that major effort will be directed toward getting the best possible equipment

available for use in the swiftest possible fashion. Thank you again for the opportunity to speak here today.

MS. EBERHART: Thank you, Miss Gregory.

The next speaker is with the FDA in the Office of Regulatory Affairs--Miss Elaine Cole.

OFFICE OF REGULATORY AFFAIRS

MS. COLE: Good morning. My name is Elaine Cole and I'm with the Office of Regulatory Affairs, ORA, the field part of FDA. And, in particular, I'm the director of the Baltimore District, which covers Maryland, Virginia, West Virginia and the District of Columbia.

The Office of Regulatory Affairs, the field part of FDA, works cooperatively with all of the agencies, centers and other major components to inspect the industries regulated by the agency, to collect and analyze samples. We're the agency's consumer complaint, public, visible component. We are also involved with recalls, tracebacks, national disasters, flood, hurricanes, a whole variety of public health promotion and protection activities.

With respect to the inspectional work which we do, the Office of Regulatory Affairs does both GMP, good manufacturing practice inspections of medical device manufacturing facilities and preapproval inspections where they're necessary for products regulated by CDRH.

With CBER, and particularly more so since the

advent of Team Biologics, which Mark Elengold mentioned, we have been involved in doing the GMP inspections of the licensed in vitro products and we have for several years participated, where we have staff available, in joint inspections led by CBER for proapproval of applications for products they regulate.

The Office of Regulatory Affairs, with CDRH, has had some experience in experimenting with new ways to try and cover industries where the amounts of resources available is limited and where there's also a desire to be able to make decisions about the status of products expeditiously.

We have been active participants with CDRH in the medical device industry initiatives, which includes things such as preannounced inspections, annotated 483s. We are the part of the agency that is most involved on a day to day basis in the issuance of warning letters, and therefore we are involved actively in the medical device initiative to pilot different warning letter issuance proposals.

I'd like to mention partly why Baltimore District in particular has an interest in this public meeting, aside from enhancing our symbiotic relationship with CBER. Baltimore has been involved for many years in a group with CDRH, which does have some CBER participation, called the IVD Roundtable. It's a group of two to three dozen

individuals who get together roughly quarterly and discuss issues related to the IVD industry. We also have been the only ORA field laboratory up until last year which was involved in the analysis of samples of CDRH-regulated in vitro diagnostics.

I would like to mention, as chair of ORA's Field Biologics Committee, that we took great note of the concern that the public and the industry raised at the 406(b) meetings in California and here in D.C., that there seem to be differences in how the agency regulated various products that were devices and IVDs.

Certainly when we go out and inspect firms which manufactured both licensed and unlicensed products, we've had questions in the past about do the 820s apply? Don't they apply? What do I have to do? What do I have to do for that?

And as Team Biologics has evolved and the lead role for GMP inspections of IVDs regulated by CBER has switched to ORA, it's been a bit of a learning curve for some segments of the industry. We can now say that we are inspecting both the licensed and the unlicensed IVDs in the same fashion. So we have already done a considerable amount to harmonize the coverage of the IVD industry.

With respect to other comments that we have had from the industry and from our own people, the desire for

training certainly and what is required and why so that our folks don't spend more time than they need to covering a particular product or an issue and so that the industry is aware of what the standards are or at least has every opportunity to be aware of what the standards are before someone shows up on their doorstep to inspect them is something that is terribly important.

We need, as an agency, to focus on expediting the decision-making process for product approvals, but similarly, if we only focus on the application itself and don't focus on the quality assurance and quality control systems under which those products are made, we're doing the public and the companies a disservice.

It's terribly easy to cut training in an era of budget tightness, so I would encourage CBER to not forget the folks in ACVA and the public meetings such as this particular venue and some of the other outreach meetings they've already had with the IVD industry.

We know that you can't always do things the traditional way because of the changes in the workload and the increases in statutory mandates and other information that we receive from the public and the Congress of their expectations.

What we would like to suggest would be number one, that it's terribly important that the agency maintain a

regulatory science base. If we do not have the ability to analyze products in the agency, if we do not have the ability for scientists to understand the technology that they're asked to assess, then we do the ethical manufacturer and the public a great disservice. So I would encourage CBER to continue to maintain a scientific base to facilitate product approval decisions.

With respect to the Team Biologics activities, those inspections of the industry currently are done by ORA investigators in conjunction with a CBER product scientist. You've heard other speakers say that it's important for the scientists to get out of the Rockville Pike area and see what's happening in the industry. Certainly CBER, like other centers, has benefitted through that process and we're always delighted to have CBER scientists participate.

We recognize that you can't clone people yet and you can't have them reviewing the application concurrently with being in the plant. That's always a tough decision to make. But we have been very appreciative of the CBER scientists' support when we've called them for a consult or had them along on an inspection.

I would mention also with respect to inspections--I should have said this earlier--that we're also the organization which does the day to day inspections of the software control devices regulated by CBER and by

CDRH and certainly the questions of software validation come up no matter which center you're dealing with. Certainly any of you who have tried to hire people who are computer literate know that that's not an easy person to find, let alone keep on your staff.

I don't have any good answer for that problem but certainly when the agency does have any new guidance with respect to what is or isn't required for validation of a software system, a public workshop or some kind of cosponsored presentation with industry would be of tremendous value to firms which are developing products and to our own people in the agency, to make sure that we don't inspect differently from the standard that industry is using.

We have found that the CBER web page, as many of you have noted, is a terribly useful piece of information to find out what's happening in the agency. It is not terribly obvious how to tease out CBER-regulated device information from other CBER products, but it's not impossible.

If there's something new going on in the area of devices or licensed IVDs, it might be useful to have that information categorized by a subheading or key word so that people who are not interested in other aspects of CBER requirements could find things more simply.

I'm technology-compromised. I asked my

eight-year-old how to do it. So I suspect that other folks who are busy may be similarly technologically compromised.

With respect to the urge to make the CBER workload more easily accomplished, the only caution I would add in the question of reengineering is it's very, very simple to say well, we won't do it; somebody else will do it--some other part of the agency, some third party. However one changes the process, it's terribly important that we make sure that the new process is actually one which can be accomplished within available resources.

The resource example I can give is with respect to the CDRH-regulated medical devices. If you look at the compliance programs for GMP inspections for that entity, you will see that there is a logical triage of what kinds of products to cover first and it gets down to the products which you cover if time is available. Well, those products don't get covered very often.

So if, in fact, the best idea for the agency is for CBER to no longer cover certain kinds of activities or, for example, to condense what information is submitted to them and have the information covered during an inspection, recognize that that has an impact of lengthening the time that an inspector will be in a facility, which is not necessarily something that the industry really likes, either. So you may get what you ask for. You may get

somebody there longer in your plant.

Certainly ORA, like CBER, is committed to the letter and the spirit of the implementation of FDAMA. We have made a number of changes--grassroots meetings, greater public access--to try and make ourselves more user-friendly. I find that I get fewer calls from industry now about items that they're concerned about that they think we're terribly doing wrong than I did two years ago and I think that if we continue through our Team Biologics activities and through the Medical Device Action Plan which ORA is working with CBER on, that we will come up with a process which both serves to protect the public health and delays how much time everyone feels an increased frustration level from not getting through the end of their in-box. Thank you.

MS. EBERHART: Thank you, Miss Cole.

The next speaker is Mr. Derek Link. He's from the Gay Men's Health Crisis in New York.

PATIENT PERSPECTIVE

MR. LINK: Hello. Good morning. My name is Derek Link. I'm from the Gay Men's Health Crisis in New York City. We are a large medical and social service provider in New York City for HIV care and support. We were formed in the summer of 1981 before the epidemic was named and HIV was identified, but since that time we've taken care of a third of the epidemic in New York City, both in a medical clinic

and a number of social services--child care, hot meals, et cetera.

Our interest in the FDA has historically been about drug development and that's the area of the FDA that I am the most familiar with. But recently we've become interested in some device issues and that is what I want to talk about today.

Specifically I want to talk about our experience with our testing center. And I want to thank Dr. Branson from the CDC for touching on many of the issues that I also want to address, but I want to talk about it from a slightly different perspective.

I hope you will grant me the indulgence of having a sort of single-minded focus on HIV right now. Even though it is World AIDS Day, I know that there are much broader issues in question here today. I'll leave it to you to draw out the larger implications of the comments I have to make.

About six months ago I was asked by our medical director, as well as our board of directors, to look at our HIV testing center. The goal was to figure out how to implement more rapid testing protocols in our center.

There is a rapid test currently available--it has been available for a number of years--but it is a blood-based test. We were particularly in--we have a van and we're particularly interested in implementing a mobile

testing unit that could go to health fairs around New York City and other areas to make testing more available.

The main goal is to have a rapid oral assay for HIV, an oral test that would not require sending the sample to a central laboratory, the way that the current oral tests operate. And this led us down the road of medical devices.

Let me say that it's very important that we develop these oral tests for a number of reasons. One of the key issues has been the standard to which they should be held. We recognize that some of the products are not as accurate as the standard ELISA and Western Blot tests. We obviously need the standard assays to be very good, because they're screening the blood supply, but I would just say that I think ambiguity is okay and I think a relaxed standard is appropriate for these tests.

Clearly we want them to be as good as they can possibly be, but people deal with ambiguity all the time in their lives. Any woman who's had a mammogram realizes that there are occasionally ambiguous results that need to be followed up with other tests.

I think people can handle that with HIV and I hope that the FDA will consider that as they look at what the standard needs to be for a rapid oral assay.

Clearly the implications for a rapid oral test for the international epidemic are profound and could be

extremely useful in many parts of the world.

And I think the other issue here is the small companies who are developing these products. It's very expensive to develop new devices and new drugs and I think the fact that a lot of these products are coming from smaller companies, that needs to factor into the decision somewhat because they do not have the capital of a Johnson & Johnson or some other major firm and it's too important for these products to come on the market for us to ignore the fact that many of these small companies do not have the resources for extensive, long-term research programs in the same way that larger companies may.

So those are my thoughts about the rapid tests. I hope that they can be a priority for this agency.

The other thing that became really clear is that this is a relatively small problem. I mean, we obviously have the ability to diagnose HIV and to screen the blood supply. So we're not talking about a huge issue. It wouldn't be a tremendous breakthrough but it would be extremely important for the people who are undiagnosed, for the people who tend to be quite young--it tends to be young adults and adolescents who we're talking about.

So the scale of the problem also needs to be considered and balanced in a way. And I could imagine there are many other scenarios where the disease or the affliction

is a relatively small one but where product could be quite important.

The other thing that was really surprising to me is the large number of unapproved rapid test kits that are available. We can essentially buy any test kit that we want. There's one approved rapid test but there are 15 that are routinely available and the unapproved ones are much cheaper, for obvious reasons.

I don't know why this happens. I don't know what it really means for the regulatory system but just getting back to the ambiguity point, if you have these large numbers of tests that are being sold relatively freely and their accuracy has never been established by the FDA, there's an inherent ambiguity in that system already.

So I don't know what to do about that but it is a problem. The standard test costs about $9 a pop and the other ones, you can get them for about $1.50. So it's a significant cost savings.

The other issue I want to talk about is not about rapid testing but another issue that's really key right now in the evolving world of HIV medicine and that's these phenotypic resistance assays. They're becoming available more so in the last several months. It's a potentially very important breakthrough for us to be able to use these assays to help people determine what drugs to switch to after

they've been on a regimen for some time.

You can do them right now. They cost about $800. There is really no standardization or regulation of these tests. Certainly they need to remain available but there does need to be some kind of regime to standardize this so people how to interpret the results and also so they can be reimbursed. Nobody is paying for these things right now and they're extremely expensive, so it's only the very well connected or well paid who are using them.

I want to make one comment about a general FDA issue that is not necessarily specific to this discussion but one that I like to raise at every opportunity and that is the need for greater sunshine in the process. I appreciate the ability to come here today and the public meetings run by the FDA I think are extremely valuable.

I do, however, think that information given to the FDA by a sponsor should be public information. This is information that is about products and drugs that are used on the American public. I think that it should be available to people so that we know what's going on.

So I know that's not going to happen tomorrow but it is something that I think many patient groups have a desire to see.

So I thank you for your indulgence and your time and the best of luck in your endeavors.

MS. EBERHART: Thank you, Mr. Link.

The next speaker, and I have to apologize if I mess up your name here, Dr. Johannes Lower from the Paul-Ehrlich Institut.

EUROPEAN COMMUNITY (PAUL-EHRLICH-INSTITUT)

DR. LOWER: Thank you very much for the great pronunciation of my difficult name. Thank you.

First of all, I would like to thank CBER and especially Kathy Zoon for the invitation to talk to you today. And I think my task is to widen the perspective to the European approach or to the approaches taken in Europe.

The present state--and I will only focus on in vitro diagnostics and will make only a few comments on medical devices in general--the present state in Europe is that in every member-state, and the term member-states means member-states of the European Community--in every member-state there are different laws, regulations or administrative provisions in force for in vitro diagnostics.

In some countries, for example in Germany, in vitro diagnostics or some in vitro diagnostics are taken as medicine products, as drugs and are subjected to the German drug law. In other member-states there are no regulations at all. For example, in The Netherlands you can go on the market without any regulation. In France there are also relatively stringent regulations. Screening tests are well

regulated in Italy and HIV tests in Austria. That is an overview.

I would like to show you the approaches in Germany. There are only a certain number of diagnostics which has to be regulated by the competent authority, and this authority in Germany is the Paul Ehrlich Institut. I'm a member of this institute.

These are the tests, the diagnostic tests which have to be subjected to our licensing procedure and I would like just to focus on the tests for HIV, hepatitis virus, for example, blood groups. There are also quite a number of other tests but this will change in the future.

I would like to mention here that only tests based on an immunological reactions, on antibody antigen reactions, are subjected to license. For example, tests which use nucleic acid amplifications are not subjected to license in Germany at the moment, but this will change in the future. There are efforts to change the law and I hope that this next year, by the middle of next year or so, nucleic acid amplification tests for testing HIV and hepatitis virus will also be regulated, especially in view of the fact that our institute has requested from all blood collection centers to perform HCV nucleic amplification tests from the first of April of next year.

Which is also not subject to these licensing

procedures are the equipments, the machines used for the tests and also not the software. Equipment is only indirectly tested in the sense that in experimental testing of in vitro diagnostics, these tests are, of course, performed with proprietary equipment. But direct testing or direct licensing of the equipment is not performed and also not for the software. These are regulated as medical devices and I will come to the principles of these regulations a little later.

The emphasis in our institute is indeed put on the licensing of the product. These are the principles which have to be met in licensing applications. We need quite a number of investigations on a new test which have to be conformed in comparison with already-licensed tests or a test which is well documented at the Paul Ehrlich Institut. We need extensive studies on discrepant results and quite a number of cross-reactive or interference samples have to be tested.

In the next two slides I show you also requirements for HIV-1, -2 screening assays. We asked for 4,000 consecutive blood donations. Consecutive means that there cannot be any selection of negative donations or it has to be consecutive in one or more centers. We need the test on 400 clinical specimens and on 100 potentially cross-reactive samples.

And to test the sensitivity, 400 anti-HIV-1-positive samples have to be tested, 200 anti-HIV-2-positive samples and investigation on the so-called high-dose hook effect, subtype O samples have to be tested and all the other subtypes if they are available. And, in addition, 20 seroconversion panels have to be studied.

This again emphasizes that we think that the characterization of the test, of the performance of the test is the most important part in the licensing. I have to say that there's also some inspection on good manufacturing procedures in Germany and in these inspection also members of the Paul Ehrlich Institut are involved.

But I'd like to say again it's more important to show that the performance of the test is as good as possible or, to say it in other words, we do not believe that--or otherwise we would not accept consistent, reliable reproducible production of a bad assay. That means that the performance of the assay is in the first place and let's say quality assurance is in second place.

Some type of consistency testing, of course--I've forgotten one point here. You can imagine that it's quite work to evaluate the applications and also to, of course, make these applications. We have to perform these reviews in a seven-month period. This is by law. But I have to

admit we will not meet these deadlines. Usually we need around 12 months for a licensing procedure but this is, in part, due of course to the quality of the applications and also of the interest of the applicant to answer our questions. We have examples where it takes years until we get the response by the company.

I have also to say that we get fees for this evaluation. These fees have been increased two years ago and I have to say that these increased fees are challenged by the industry at the court and we expect an answer from the court I guess in the year 2001.

A part of the consistency testing, of course, is what we call in Europe official batch release. That means an official release lot by lot. This is done by the control of the production protocols, as well as again some experimental testing.

We put a lot of effort into make these official batch release as short as possible. I know for some manufacturers at least we can perform this batch release in less than seven days--seven days, not working days. Again we get fees for this work.

I believe in the next three slides I would like to show what in our opinion is a very important and I guess also to some extent a new approach, what we call reevaluation of the test.

You know, the tests are licensed according to the state of the art when the application was made. But the technology is moving, is improving all the time. And for this reason, we perform a reevaluation in certain time distances--for example, every two years or so.

And we do it most extensively with seroconversion samples and we test these samples and look where the first sample is positive as the best assay. For example, in this case, and these are HIV tests, test number 3 was positive already at this date of the seroconversion panel. Then we measure either the number of donations missed or the days missed. The days are the theoretical shortest day, smallest number of days which could not be recognized.

For example, this assay here recognizes in this seroconversion panel the positivity eight days later than the first, the best assay or, in this case, the three donations after the one which has been detected first.

And if we do perform such tests for HBS antigen assays, HCV, anti-HCV and anti-HIV assays, we have obtained the picture I guess last year or a year ago or so, that you can see quite differences in the biological sensitivity of different assays. You may notice that all the HIV assays are very sensitive. They are very close to each other and this may be due to the fact that we have performed such a reevaluation already four years or five years ago.

But you see the great diversity between hepatitis B surface antigen assays and anti-HCV assays and you can see an average delay in recognizing the seroconversion up to 11 days for some assays.

You may notice here the red dots. That means that these assays have been taken from the market after this reevaluation study I have to say more or less voluntarily. The yellow points point to assays which will most probably not pass the next reevaluation assay.

This figure shows again anti-HIV tests and these are the tests I have already also included in the previous slide. These are two tests used in another country and you may notice that in this country, at least, these tests have a much lower biological sensitivity than the tests which have been licensed in Germany. You may also notice here that we, at the time of this survey, we had 17 different screening assays on the market.

So I have to expand a little bit on the present state in Europe. Of course, these discrepancies between member-states was recognized and since a couple of years already there is an effort at the Commissioner to introduce and harmonize law and harmonize ways of regulating in vitro diagnostics.

This directive, as the laws made by the European Commission are called directives, this in vitro diagnostic

directive has been finalized. It's already signed. We expect the publishing of this directive every day. It was not published until the end of the last week but it will be published I guess in December. That means it will come in force in mid-2000.

And in this new approach--in also Germany and also member-states have to follow this new approach--in vitro diagnostics will be regulated as medical devices and no longer as drugs.

The key elements of these medical device directives are listed here. For all directives are essential requirements defined. There is a request for the use of harmonized standards and with respect to in vitro diagnostics, so-called common technical specifications will be developed. They are not yet developed but they will be developed and I guess they will reflect to some extent the requirements, for example, put forward by the Paul Ehrlich Institut.

Devices will be classified and I come back to this classification a little later.

The basic approach is that there is a so-called conformity assessment and this conformity assessment can be done in different ways and these different ways are described as modules. There is a combination of modules which has to be followed for the conformity assessment.

If this conformity assessment was positive, a so-called CE mark--CE means the French word for European Commission--CE mark can be added to the product. This allows marketing of this product of this in vitro diagnostic, for example, in the whole of the European Community.

To some extent the main responsibility is with the manufacturer in this respect but for certain types of diagnostics a so-called notified body is involved. Notified body is the name that comes from the notification of this body to the European Commission. This body can be a private one; it can be a public one. This body has to certify that the conformity assessment was performed properly and had a positive result.

If a product, if an in vitro diagnostic product is on the market, it will be controlled and this will be done by a competent authority, which is usually a public organization.

These are the names of the different modules. I realize that it is difficult to understand what they mean and even for me it's still complicated to explain it in great detail. For example, the EC type examination is very similar to a licensing of a product and it's more easy to understand what a full quality assurance system or a product quality assurance system is.

So how are in vitro diagnostics classified? There are two classes. Class 1, there is no list for Class 1 because they are all in vitro diagnostics which are not Class 2. Class 2 are listed in a so-called Annex 2 and are divided in two lists--List A products and List B products.

List A products are the products which are most stringently regulated and these are tests used for screening blood donations--determining the blood groups, different blood groups and tests for the detection, confirmation and quantification of human specimens of markers of HIV, HTLV, hepatitis B, C, and D.

You may notice that in this wording there is no distinction made between screening tests and diagnostic tests. I think this is indeed the policy not to differentiate between these two types. So that means that all tests used for the detection, confirmation and so on of HIV markers and so on has to be licensed according to the regulations for these products which are called high-risk products.

I have a list of List B products but I guess these are not of interest, too much interest here. If you want to see it, I can show it later.

How are these products regulated in the future? That means with the beginning of the year 2000 or the middle of the year 2000, there are two possibilities. This is one

of the basic approaches, to give the manufacturers at least two different possibilities to perform a conformity assessment.

This way for the List A products you have two possibilities and I have to say on the paper; in practice there is no big difference between the two approaches. One approach is to have an EC-type examination which is, as I mentioned already, very similar to the license of a product as it is performed today in Germany or I guess also here in the United States.

And, in addition, you have an approval of the quality assurance system by a notified body--it's also done by a notified body--and a batch release procedure. Official release lot by lot has to be performed until a declaration of conformity can be given.

And the other possibility is a so-called EC declaration of conformity with the full quality assurance system but in this system there's also included the EC design certification, which also means an evaluation of the performance of the product. And, in addition, there is an approval of the quality assurance system and also batch release procedure.

And again, of course, all these things have to be done and have to be paid by fees by the different companies.

So I will close at this point. I hope I could

give you a small insight into the situation in Europe. Thank you very much.

MS. EBERHART: Thank you very much.

We're now going to take an hour lunch break. The cafeteria is on this floor, that way, for those of you that don't know. And I'd like to return at--I believe it's about a quarter till 12:00--in an hour.

[Whereupon, at 12:45 p.m, the meeting was adjourned, to reconvene at 1:45 p.m. the same day.]

A F T E R N O O N S E S S I O N

DR. DONLON: Welcome back. Even though the agenda has allocated half an hour to my presentation here I will not be taking the full half hour, in fact be taking about ten minutes to focus on some areas that we've heard about in the past and are going to look at in the future. And then following my brief presentation there will be other presenters putting forth their comments and observations.

I just want to briefly review, and I want to make it clear at the outset, I'm not going to present the Device Action Plan here. We're in the process of developing that, and this meeting is part of that process, and the comments that we've heard here this morning and basically the transcripts that we get from this meeting will be disseminated among the core team members for review and discussion, and those suggestions will be evaluated and if necessary put into our action plan.

Also I would remind individuals that the docket for this public meeting will remain open for at least two weeks and perhaps longer so that if you have time to reflect on some of the comments or discussions you've heard you can always submit a written comment to the docket. Unfortunately I don't have the docket number with me at this time, but there will be an open docket on the CBER Device Action Plan public meeting that will be at least for two

weeks and perhaps longer available.

Just a brief kind of history of where we've come to at this point. Kathy mentioned this morning in her speech that the public meetings that took place in late August and early September had raised certain issues regarding how CBER had regulated or was regulating devices. In addition, clearly during the past year we've been looking at the FDAMA initiatives, specifically the device FDAMA initiatives and how they impact on our regulation of devices. And the third element I think that has kind of began to focus us on the need for a device action plan were elements that were raised by Mark Elengold in his presentation on our clearly restricted resources and our limitation on resources and the need to apply what resources we have in a very efficient way.

So I think those primarily three factors coming together have, I think, made it clear to us at CBER that for our interests of utilization of resources, implementation of FDAMA activities and addressing some of the concerns that we heard in the public meetings, that a device action plan will target us on those needs.

Just a few comments about the FDAMA process. The FDAMA had several, more than several device initiatives for which the Center for Devices had the lead on developing regulations and guidance documents for the FDAMA initiative.

They put together a tremendous team effort in the Center for Devices and have I believe met all of the goals that were intended in the FDAMA law for getting out documents of that kind.

During that process Kathy had assigned me as the liaison with the Center for Devices regarding FDAMA actions, and since February of last year I have attended the weekly steering committee, the Center for Device steering committee meetings, who oversaw their FDAMA initiatives and received the documents, the draft documents, proposed documents and circulated them among the appropriate people in the Center for our review and concurrence.

So we have been in the loop with the FDAMA documents that the CDRH has had the lead on, and to further document that, if you will, we are having current preparation of a Federal Registered Notice that will basically very simply say that given the particular documents that were developed at CDRH relative to device actions on FDAMA initiatives that CBER is in concurrence with those and will use those as our implementing documents.

So I just wanted to make clear that there have been working relationships on the FDAMA issues established during the past year and that we intend to continue those.

Kathy showed this slide earlier. Basically I'm showing it to remind people that these are the core team at

CBER. There are also as you know Elaine Cole who is with the District; Lillian Yu who is really Lillian Yin, who is with the Center for Devices currently; and there are a number of other people whose names are not on the list. Kimber Rector from the Center for Devices has been helping us in this regard.

So the core team is including not just the CBER people but their relative counterparts if you will at the Center for Devices to coordinate our action plan.

Basically we conceive the action plan to be targeted to these three main areas, and I'll briefly mention how we're structuring that to accomplish this. Clearly we are aware of the fact that we need to have harmony with CDRH regarding device issues in regard to the policies and procedures and guidance that are available there.

We recognize that we have a different set of devices that have different intended uses that have different risks and different benefits, and so -- and different technical needs -- so that we recognize, and devices also recognizes that in regulating devices you take those into consideration and so that there's no expectation that we would be regulating a particular device any differently that the Center for Devices would in the sense of applying the concerns for risk and benefit and technical expertise.

As I mentioned before, the harmony with the Center for Devices has already started, if you will, in regard to the FDAMA documents, and we also have plans within the tentative device plan to facilitate mutual training between the two centers so that our staff can be trained at the Center for Devices and we can have people on the Center for Devices on detail to our center to basically experience and bring their expertise to our center for device issues.

Also in this regard I should mention that one area the action plan will address is the intercenter agreement. There's been an intercenter agreement with the Center for Devices, CBER and the Center for Devices, for more than ten years. The first one, I'm not sure of the exact date of it, but Dr. Aziz from devices can probably remember that, he's been there 50 years is it?

There was an original intercenter agreement probably formulated back around 1984 or thereabouts. That intercenter agreement was revised in 1992, and it's appropriate to reevaluate and revise that again so that certainly would be one element of our action plan, is to look at the intercenter agreement and how we are working together in dividing up the devices and the guidance in that regard.

The Device Action Plan also clearly needs to address the procedures and performance that we apply here in

biologics to device reviews. We have attempted, although lacking the resources, not been as successful in, we have attempted to target device reviews in the same context of some of the user fee reviews. However, we are really restricted there because clearly there are requirements with the user fee products for the review times that if they're not met have consequences.

Without having user fees applied to the device area we've not had those penalties or consequences available, however, we have been trying to maintain basically a targeted time frame that would be consistent with the PDUFA time frames. But given the limited resources in the device area, that's very difficult to achieve.

However, we will be looking at the policies and procedures that the Center for Devices has utilized relative to their re-engineering where they've had severe restrictions on their resources and basically through risk assessment and prioritizations have been able to target their resources to critical areas in the device industry.

We don't have as many devices as the Center for Devices to regulate, and that may be a limitation for us because we don't have a wide discretion on a lot of class one devices that we can basically exempt.

Although we've looked at that in the past, we've looked at, as the Center for Devices has exempted their

class one devices, we've reviewed our class one devices with a similar intention.

And another area that has come out this morning in comments also is the area to facilitate communications. This is a broad statement, it's not just communications within the center, not just communications between the center and CDRH on issues, but also communications with industry and communications with the public. We want to try to in our Device Action Plan make as much of our activities transparent as possible so that through guidance documents, through meetings, through training sessions, through whatever, through web sites, whatever may be available, that the activities that we use to regulate devices is made clear to the industry, to the public and we facilitate our communications with the Center for Devices on technical issues of mutual interest, for example the software.

The general principles I think are fairly straightforward. Clearly the Device Action Plan will address the issue of consistency of policy and procedures for regulating devices consistent within the center and consistent between the centers so that again this comes to the issue of transparency so that there is a clear understanding from a manufacturer's point of view or from the public point of view of an expectation of how we're going to implement a particular review or guidance document.

There is clearly needs for coordination, coordination with the center, coordination between the centers, coordination with the field on the inspection issues that were mentioned by Elaine Cole this morning. Again, this addresses I think the issue or resource utilization where with better coordination we can basically make more efficient use of the resources we have.

Cooperation goes along with coordination. Basically if you have restricted resources you need to respect the expertise and the area of impact of other areas of the programs such that you're not duplicating or overlapping your program operations, and so you depend on cooperation with other elements in the center or other elements in the agency or elements in the field in a cooperative mode so you don't have to reinvent the wheel or duplicate your activities.

Efficiency addresses the issue of review processes in which we may need -- we will need to be because of the reduced resources more efficient, trying to again through maybe communication and guidance documents reduce the number of cycles of the review process so that we can quickly come to a termination point, if you will, without having to reiterate or reprocess may times over.

Training I think has an impact here. If we have the proper expertise and training of the staff that also

facilitates the efficiency of the review process. Delegation of decisions and assignments is another way of making it more efficient.

Relative to our user fee program for the biologic user fees, we have over the past year or so implemented a manage review process which certainly can be applied to the device area in which critical decision points in the review process are held accountable.

Prioritization is certainly another area where we can gain both efficiency and utilization of resources. We certainly want to make sure that we're applying our resources to the most highest priority devices and the highest priority public health issues, and therefore we need to look at again areas of where the resources will be applied in that context. So there may be a process here in the Device Action Plan of basically evaluating the devices that we regulate in the context of safety and efficacy or risk assessment and making a priority assessment as to which devices are going to get the resources in a way that we're assuring protection of the public health.

And finally, the principle again of transparency. Again, this addresses the issue of communications as well, where if as was mentioned in some of the comments this morning, if we can be more clear in our guidance documents, in our meetings, in our training such that the expectations

of industry and the public upfront are very clear, and it's also clear what our process is and what the procedures are, that that will facilitate the evaluation process and the approval process and perhaps also reduce the number of cycles of review that may be reiterated on a particular device.

So the action plan is under development basically. This meeting is one part of that where it's part of the communications issue of reaching out and listening to what the concerns are, what the suggestions are, and we can look at the last slide I think. And as an input to our deliberations over the next couple of weeks, next couple of months to help us formulate and focus on those critical issues that you as the public or you as the industry feel are critical points that need to be addressed by this plan.

This plan basically as I foresee it evolving will be somewhat specific. It will be fairly focused. It will have fairly I think clear action items and clear responsibilities and clear time frames such that roughly a year from now we can go back and look at the accomplishments of the plan and see whether we met certain objectives of the plan in a very objective way.

So it will take us a couple of months to I think to formulate a very clear and specific action plan, but it will be I hope an effective plan of utilization of our

resources to develop more efficient but safe review practices.

Again, as we've heard this morning this meeting is primarily a listening meeting for us to hear what your suggested inputs and recommendations are. We like to hear your experiences with the Center on Devices, your concerns about where we're going or what we're not doing, expectations that you would have relative to the Device Action Plan and certainly any suggestions, some of the suggestions that have been made this morning, we'd certainly welcome any more.

Again, reminding you that the docket is open for at least two weeks and possibly longer, so you can always reflect on what you've heard today and submit written comments which we will then take into consideration.

Thank you.

MS. EBERHART: Thank you, Dr. Donlon. We're now going to move on to the presentation and prepared statements, and the first speaker is Mr. Edward Wilson from Hogan and Hartson.

MR. WILSON: Good afternoon, everybody. My name is Ted Wilson. I'm from the law firm of Hogan and Hartson. I'm an attorney there.

Our firm represents a number of clients who are interested in today's discussion. Many of those clients

manufacture in vitro diagnostics or blood related devices or accessories that are regulated by CBER, and this presentation which I'm going to briefly go over is an attempt to offer some suggestions about regulatory reform that are supported by a number of our clients who make those products.

We also represent numerous companies who manufacture medical devices that are regulated by the Center for Devices and Radiological Health, CDRH, so we have I would say a fair amount of experience dealing with the agency with respect to how it regulates medical devices. Next slide, please.

The first thing I want to do is thank FDA for holding this meeting today. I think it's a very important forum to be able to discuss a very significant issue to the industry.

The first thing that we recognize and that it is important to recognize, which was reflected in some of the comments this morning, is the fact that CBER does have a number of conflicting pressures put on them on a daily basis. You have congressional oversight; I can imagine that being in a congressional hearing would be similar to this where I'm looking up at this vast array of audience that's sitting very high above me. I would imagine though it would be a very daunting and terrible experience.

Also public concern over safety, obviously the public is very concerned about the safety of the blood supply and the products that CBER regulates. Also, however, there is the public desire to have access to the state of the art technology, so that you have a conflict there between wanting the most state of the art technology available with the interest of having the safest products available as well.

Industry's desire to bring new products to market in a timely manner of course is another conflicting interest, or if you will, another competing interest that CBER has to deal with. But against this backdrop I think we're all here because we believe that change is possible and that change is necessary with respect to how CBER regulates medical devices. Next, please.

We believe that CBER should consider embracing some very important re-engineering activities that CDRH has already implemented, in part on their own and in part in response to FDAMA. And we believe also that a lot of what CDRH has implemented is transferable to other centers such as CBER.

For example, you've heard already talk about modular submissions, which is the ability to put in submissions in stages so that when the manufacturer is ready to put in the device description or the manufacturing

information, that can be put in and the agency can review it, the issues can be put to rest and then you move on to other parts of the submission so that it's done in a timely fashion.

Ninety-day reviews for 510(K)s as many people are aware, CDRH has made significant improvements in bringing down the review times for 510(K)s, and many 510(K)s are reviewed well within the 90-day framework. And we'll talk a little bit later about how we think that can be done.

You've heard a lot this morning and this afternoon about interactive reviews. Our experience in dealing again with CDRH has been that the interacter reviews are instrumental in preventing major delays in the review process and in actually meeting those 90-day requirements for 510(K)s because if you have a simple question about, I don't understand this statement in the labeling or I don't understand exactly what this component does in your product, it's so much easier to pick up the phone and get those things clarified immediately and not have to wait for a letter to be generated, not have to wait for the company to respond formally to that question.

Focused meetings to resolve big issues, once again being able to sit across the table from the reviewers and hammer out those issues that are deal breakers or potentially deal breakers, making sure that everyone

understands the resolution to those big issues and those problems before we move forward. All of those things can lead to shorter review times, which we've seen with your sister center, CDRH.

Another issue that's come up in my discussions with a number of our clients is making sure that scientific issues are -- once scientific issues are resolved they are put to rest to the extent that additional information doesn't come up and challenge those resolutions. If scientific issues are resolved they should be resolved and you should move forward with the rest of the review instead of revisiting those issues once additional information comes forth that's not relevant to those issues. The next slide.

Another re-engineering activity that we think is important is assuring that all device related provisions of FDAMA are encompassed in CBER's policies and procedures. We've heard time and time again today the emphasis on FDAMA and the fact that CBER is looking at FDAMA and the guidance that that's providing as well as the requirements that are in that statute.

But there are some very important parts of FDAMA that are very relevant to the review process, and that are very important in trying to expedite reviews. One is the provisions relating to agreement and determination meetings, which are agreement -- agreement meetings and determination

meetings are those meetings that you have before, in many cases, the IDE phase or at least before the PMA phase, which allows the agency and the industry to come to agreement on what are going to be the requirements for establishing effectiveness, what are going to be the requirements for the number of patients that are going to need to be included in this trial.

And this helps avoid the moving target syndrome, the syndrome whereby if staff changes within the agency or as time passes if some requirements change, that you at least have established some agreements upfront as to what the requirements are going to be so that it's not a moving target for industry, so that after they've spend thousand or millions of dollars doing a study they don't find out that the target has moved.

Another important requirement in FDAMA is establishing the least burdensome means of demonstrating substantial equivalents or effectiveness for devices. And this means that what congress said here was that they want the agency to make sure -- obviously it goes without saying that the products have to be safe and effective, I mean no one is challenging that. But what congress is saying here is that the agency needs to work with the industry to determine the least burdensome means of demonstrating substantial equivalents or effectiveness. Not the most

burdensome or the most ideal in every situation, perhaps, but what's the least burdensome to still get a product that's safe and effective or that is substantially equivalent to its predicate device.

FDAMA also includes language that suggests that the agency should consider what post-market controls can be placed on devices or manufacturers to lessen the data requirements that are required for premarket approval or premarket clearance. So we and the agency needs to consider what kinds of post-market controls would replace some of the premarket requirements.

A combination of these re-engineering activities can dramatically improve the process of reviewing device applications. I don't think it's one single factor that does that. I think it's a number of things working together, and all these initiatives put together will help with that process. Next slide, please.

The next recommendation is another one that you've heard many times today, which is improving communication with industry. Many people have found it difficult to obtain guidance in response to direct questions regarding applications of the regulations. You know, our experience in particular has been that we're often referred to the Office of Congressional Affairs which leads us through a labyrinth of different people and different offices to try

to find some answers to some fairly basic regulatory questions.

So it would be very helpful to us and to our clients if there was a more expeditious way of getting to the people in the agency who know the answers to these regulatory questions.

We've also heard about the web site, but I would also emphasize again that it's important to have guidance documents that are current and that are made available to industry though user-friendly web sites such as the one CDRH is maintaining and the one that you are implementing so that everyone knows the center's requirements and expectations. Next slide, please.

I think it's inherent in the fact that we have such an array of people here in the room from industry, from the agency, that we have a common goal which is that we want to make sure that the public has access to safe and reliable state of the art technology, and that we work together to help ensure that products are available in a timely manner.

It's important to remember that we all have that goal, and it's not the industry versus the agency but that really the agency has multiple customers. The customers are the public, because you have the public health and safety to protect, but also your customer is industry, because industry is out there also trying to make the public have

access to current state of the art technology that's also safe and effective.

So there's a multiple goal here, or there are multiple parties here who have the same goal. Next slide.

Some other issues to consider. One is sensitivity to intellectual property issues, and what we mean by that is that a company that has a product for a new material, antibody source for example, could create a monopoly if the product that contains that source is viewed as the gold standard by FDA, and no one else has access to that source material.

So I think that there just needs to be a greater sensitivity to the fact that intellectual property or patent issues can also play into this, and it may not be always possible or economically feasible for people to have access to source material, and if that source material is in a product that is the gold standard that can provide problems to people who are coming in after the company that has that license or who has that patent.

The next point is, is that it's important to make known the acceptable error rate for tests. The zero risk approach has to be replaced with a reasonable tolerance for error. We all want the safest and the most effective product, but the question is, is zero tolerance attainable. Is that workable. And it's important to make sure that the

agency makes known to industry what is the acceptance for sensitivity and specificity that's short of risk-free products.

And then finally a suggestion which I realize that the agency, that CBER is already working with CDRH, but one of the -- it's often difficult. I personally do a lot of quality system audits for our clients. I go in there and make sure that their quality systems are functioning in accordance with FDA's regulations, but also that it functions so that the business can function. And one of the recommendations we would have would be to bring in an outside audit team, using the approach of an independent auditor who is going to look at the quality system here in the center, find out where the problems are, where is the system clogged, where is streamlining necessary and possible given your limited resources, and then redirect those resources appropriately.

In my close-out meetings with my clients, when I finish these quality system audits I have to present to management the findings, and I have to say look, I know that you don't have a lot of resources to throw at regulatory affairs and to manufacturing quality assurance, I know that you have limited resources, but there's got to be some way that we can redirect what you have in order to make your system work, not only from a regulatory perspective but from

a business perspective. So it really -- this idea really applies to anybody who is in business at all, to make sure that their organization is operating as efficiently as possible given the resources that they have.

And finally I would like to close by saying that I think there's a tremendous amount of talent in this room. I think when you look around the room and you consider the enormous talent that exists at the agency, within industry, within organizations and non-profit organizations, all the different people who were presented today impress me as being the source of a lot of valuable information. And I think if you put those people together in a room and locked the door and sit down and hammer out how this is going to work, I think it can work and I think it will work. And I'm sure it will in my practice, and by the time I retire I'm sure it will, hopefully well-before that.

But I really do think that we have to pull on all of these different valuable people who have all these talents and sit down with them as if they were sitting in a corporate meeting and say look, how can we make this work, what kinds of things do we have to do. And I'll bet you it will work.

Thanks.

MS. EBERHART: Thank you, Mr. Wilson. The next speaker is Ms. Emily Rossiter from Regulatory Resources.

MS. ROSSITER: Thank you. My name is Emily Rossiter, and I'm a blood banker and consultant who has been working with CBER device approvals since pre-amendment days. I'm sorry Dr. McCurdy left, because I was going to say I haven't been involved as long as Dr. McCurdy has, but I do go back to pre-amendment days when biologic staff regulated devices using master files and product license applications.

Much about blood banking, our world and FDA has changed in the subsequent decades, and old practices are difficult to give up, but I'm very encouraged to think that FDA believes it is time to modernize device policies and practices. The next slide, please.

I'm joined in these comments today by the following organizations, which include both old and new CBER device manufacturers, reagent suppliers and device users: Hemenetics Corporation, Terumo Medical Corporation, Hall Medical, Design Quest, Incorporated, America's Blood Centers, Boston Biomedica who was added over lunch, basically, and an anonymous diagnostics firm.

Many of my comments during the August 14th stakeholders meeting concerned CBER's regulation of devices, and I certainly appreciate your listening then and your listening now. I'll not repeat them here. Instead I'd like to focus on the current situation, specifically with CBER device regulation; propose some principles of my own for

future policies at the agency; and suggest some very practical steps to take in the short term. Next, Kathy.

Among all the devices regulated by FDA, CBER's devices really are unique for reasons that go beyond their long history of regulation. First, there is a long history of providing clinical data to support even pre-market notifications for class two devices. Second, they are used in a highly regulated environment. Unlike other medical devices whose market clearance means they're released into the general healthcare world at large, many of CBER's devices are used in establishments that make licensed products and are inspected even more often than the device manufacturers themselves.

This provides two different GNP or quality system environments to make sure that the device is performing appropriately, and gives FDA investigators twice as many opportunities to detect a problem with a product after market introduction. A testament to the effectiveness of this environment is the relatively low number of recalls or MDRs that have involved CBER's devices over the years. Next slide, Kathy.

The device review system we have in 1998 is stressed as I think Dr. Zoon statements this morning supported. Review criteria usually follow new technology, sometimes a year or more after initial submission, and this

delays their clearance. Many device reviewer check lists or guidance, if they exist, are not well-known to industry and reviews often contain surprises even for experienced firms. 90-day reviews for premarket notifications are a topic of the good-old-days stories, and as others have explained, reviews that stretch into years keep industry and FDA perpetually out of synch.

Review check lists and questions do not reflect device classifications, device history, experience or public health risk, and all clinical data seem to be reviewed in the context of safety and effectiveness instead of substantial equivalent for class two devices.

I have often wondered if we were to assemble a list of reviewer questions -- let's go back to the last one -- I've often wondered, if we were to assemble a list of review questions for, in the case of an IVD, a class one IVD, in vitro diagnostic, a class two IVD, and a class three or licensed biological IVD, obscuring device identity and class, if we could guess which set of questions when with which test.

I think they might sometimes be indistinguishable. In an effort to standardize the review process, we may have found ourselves in a one-size-fits-all environment that doesn't recognize common sense differences among devices that keeps FDA and industry staff on treadmills and delays

the availability of approved products. Now, Kathy.

So how does a federal agency with limited resources even begin to tackle some of these issues? I submit for your consideration some principles that may provide a foundation for regulatory modernization. I cannot claim ownership of any of these. You've even heard several of them already today. They are actually from colleagues at FDA, even some of your colleagues at CBER.

Number one, harmonization is beneficial, externally and internally, and I think you've heard enough about that today. You can read my remarks if you want to hear my own defense for that.

Number two, CBER's regulatory investment should be appropriate for the potential public health risk. CBER staff should not be spending as much time and energy on the premarket clearance of class one and two devices as they do class three devices and licensed biological reagents, and neither should industry.

Objective tools such as device classification and risk or hazard analysis should be considered when creating review check lists, determining the need for preapproval inspections, change reporting and allocating scarce FDA resources.

Three, as effective quality control practices increase the need for premarket regulation decreases, or as

a recent Federal Register notice proclaimed, and I quote, "Current quality control practices and procedures may make continued active premarket regulation less necessary," unquote.

There is no more appropriate place in healthcare than blood banking to try this one out.

The next slide gives some examples of lower risk devices that could be downgraded or exempt from premarket notification. You've heard other suggestions from people this morning, and I certainly agree with their additions to this list.

Software programs that calculate, transfer data or interface instruments; automated devices with exempt manual counterparts; and in vitro diagnostics that are ancillary rather than diagnostic. And reagents, even some licensed, used with controls and inherent checks.

While we're on the topic of reagents, a number of kits currently reviewed by CBER need official device classifications assigned. I've seen clearance letters for the same products some times come back with a class one designation, and other times with a class two designation. We're confused. Next slide.

I didn't want to sound facetious, but this comment has actually been made a number of times, usually following an FDA inspection, where guidance documents for injectable

drug products were being applied to in vitro diagnostic test kits. The problem is not with the regulations, but with the fact that investigators seem to think that the regulations have only a single interpretation for all products.

I appreciate the comments this morning that this whole process at least with Team Biologics has been a learning curve and hopefully we're getting closer together on interpretation as time moves on. Also please note that licensed biological reagents of human blood origin have three sets of GNPs to deal with, and some harmonization there for this subgroup of specialty products would be very helpful.

Perhaps public health risk or hazard analysis can help us decide which IVDs may warrant the highest possible levels of environmental and in-process controls and which ones can be controlled sufficiently during use to justify a more feasible approach to manufacturing quality systems. Next slide.

When CDRH began modernization several years ago there was much talk among staff about skinny rabbits. These weren't victims of toxicology tests. Rather they were a symbol of can-do actions that were feasible in the short term in face of overwhelming challenges.

Staff knew that they were being asked to perform miracles, that is, pulling rabbits out of hats, and they

were looking for the skinny rabbits first knowing they would be quicker and easier to produce.

Using this same analogy, my last slide lists for your consideration the skinny rabbits for CBER's Device Action Plan. Number one, track and publish data on device review performance. Thank you, Dr. Zoon, for starting that this morning. And have as your goal, of course, reviewing the applications during the prescribed, in some cases statutory, time frames.

Number two, use public health risk assessments and other principles I've talked about for modernization as an objective foundation for decision-making and priority setting at every level.

Three, establish a clear appeals mechanism beginning at the reviewer and supervisor levels. Ombudsmen are necessary and very useful, but the most efficient way of dealing with problems is to begin at their source.

Finally, two good programs from CDRH should be embraced by CBER, and some of the other ideas of other speakers I endorse too. But their warning letter pilot program could prevent misunderstandings and support corrective action rather than punitive action, and CDRH's searchable data base for device codes, classifications, clearances and 510(K) summaries are extremely useful.

CBER's device information should ideally be

integrated and kept as complete and current as theirs, so that there is no need to check both places or go through tedious, sometimes endless, FOIA channels.

In conclusion, the CBER Device Action Plan staff has a formidable job ahead, but a public commitment to modernization is a very good first step. You have both cheering section and partner in the medical device industry where there is a keen awareness of the value of quality and the challenges in keeping blood products and transfusion medicines safe and effective.

Thank you.

MS. EBERHART: Thank you, Ms. Rossiter. Our last speaker for today -- on the agenda, by the way, Carolyn Jones is listed as a speaker again, but I messed up. So our last speaker is Mr. Leonard Frier, from MET Laboratories.

MR. FRIER: First, I'd like to tell you who I am. I don't have overheads. Actually I really wasn't sure about what the fit was between MET Laboratories and this group until this morning. But what it is, is we are a test laboratory, an accredited test laboratory, in Baltimore, and we test medical devices.

And under the Food and Drug Administration Modernization Act they came up with a real good thing, which was called an abbreviated 510(K). Everybody I'm sure knows what a 510(K) is, but under the abbreviated 510(K) procedure

in the Food and Drug Administration Act, the Modernization Act, a real good opportunity developed for laboratories and for a way to speed the process of getting devices through the FDA by utilizing this method.

What this method did was say that if a recognized standard, recognized by the FDA existed, that all somebody would have to do would claim that the product complied with that standard, certify that it complied with that standard and it would sort of shorten up the route to get a device through the FDA in the process of getting clearance for market.

In the way of getting this cleared, the FDA has already recognized over 400 standards. However, most of these standards are on devices, they're not on biologics, but I understand that they are looking to recognize certain standards that could be used in the -- with biologics as a method of getting biologics through the FDA using the abbreviated 510(K) route. And that abbreviated 510(K) route is a procedure that should be fast.

However, in doing that procedure you still have to show that there is a predicated device and prove that you're essentially equivalent to the predicated device. What you don't have to prove, however, is the safety and effectiveness, because theoretically proving compliance with the recognized consensus standard would show that safety and

effectiveness is covered in accordance with this procedure.

The procedure is supposed to speed up the process. However, now there is a couple of bottlenecks in the process at the FDA, and that's what I was going to sort of talk on. It's a problem that we're seeing in the abbreviated 510(K)s that we've submitted for manufacturers in getting products through with this new method.

The one is that the 510(K) still gets in line behind the reviewer in that certain panel. There should be a way that an abbreviated 510(K) finds another route through the same panel and the time that it takes to go through, if it's an abbreviated, doesn't have to wait for a device that's in front of it. It should go through faster. That would be a major significant step in having an abbreviated 510(K) really reach the market for clearance much faster than the traditional 510(K) methods.

The other one is that there's got to be -- the people that do the testing have to be recognized with a certain amount of credibility and acceptance. The FDA does not accredit laboratories, but the FDA should recognize certain accreditors that do test and certify in accredited laboratories to say that the credibility exists with that laboratory, and if they've done the tests in accordance with the recognized consensus standard there's a certain amount of impartiality that exists and a certain amount of

credibility that exists. And the FDA should allow or provide some credibility to that so that a lot of the checking that they normally have to do wouldn't have to be done normally.

You understand, the FDA in allowing the manufacturer to certify that the product complies with the consensus standard, all the manufacturer has to do is certify that and maybe give some synopsis of the test results. However, the FDA says in order to assure that the testing is done, because it isn't submitted with the package, is they give a manufacturer three days to provide this testing package to assure that all the testing was done. And their three days is a way to say that the data is there, it can't be generated after the fact, and it sort of cautions the manufacturer not to try to say that he complied when he really didn't complete all the testing.

So I think there is a lot of credibility that's got to be placed with the people that do that testing, so they recognize that.

The next thing is that the FDA must provide some limited access to reviewers to the accredited third parties that would do these testings. I know the manufacturers have an access to the FDA. However, when a manufacturer meets with the FDA it's usually a formal meeting, and a formal meeting requires a sign-in, it requires advance notice, it

requires a letter of the agenda of the meeting, and there's a lot to getting that meeting.

And I say that if the testing is done by some kind of accredited person, like they're using the pilot program for third party reviews, and accredited person, there should be some informal access to the reviewers in order for the third party to really understand exactly what has to be done, how it's got to be submitted, what date it should be there, so that when the device comes in in the abbreviated 510(K) format that it's more or less easily accepted.

And that is, you know, an idea that's in the paradigm that the FDA proposed in the Food and Drug Modernization Act that can really reduce the time to clearance of products. Now, I know of the over 400 standards that have been adopted, a lot of them don't relate to biologics, but I also understand that they're trying to look for some. And if they do get some, it would be a route to get things through, I think, in a more speedy fashion at the FDA. And my experience is all I'm relating to you in the problems that we're having with other kinds of devices and certainly if it moves this way, if the FDA could see that these problems do exist and find a vehicle to make sure that it goes through faster using the abbreviated as the route, that I think it would be of significant help.

Thank you.

MS. EBERHART: Thank you, and I'd like to thank all the speakers today, and before we move on to a question and answer period I just have a few announcements. For those of you who did not receive copies of the material or you don't have all of the parts of the material, if you could please leave a business card on the front desk and we'll make sure we get it to you. If you just write on it if you need the full packet or if you just need the partial handouts that aren't included in your packet, or if you can just write your name and address on a piece of paper I'd appreciate that.

A copy of the transcript will be posted on our web page in approximately three weeks. Once we get the disc from the transcriber then we'll have it put on our web page. And we do have a docket number that will be open until December 22nd if you'd like to submit comments to the docket. It's 98, N as in Nancy, 1002.

And before I turn this back over to Dr. Zoon, I'd like to know if anybody would like to come up to the podium to make any comments or ask any questions.

(No response.)

If you do comment on anything, if you could please stop by the transcriber desk at the end of the meeting and leave your name and affiliation so we could have that included in the transcript.

DR. ZOON: Thank you, Kathy. Well, it was a very interesting and important day. I think many of the comments that we heard from the speakers today very much echoed what we heard at the 406(B) meeting dealing with harmonization with our sister center where appropriate, enhancing communication and transparency and focusing on review performance and accessibility of procedures and clear guidance.

I think that these are all very important concepts that we will take back with us as we move on and consider the remaining comments that come into the docket.

I want to thank everyone for coming here today. I think this was enormously important. I want to thank those of you who had an opportunity to speak and those of you who came to listen, and I want to particularly thank all my staff for coming and listening very intently to the issues raised. I know it's very important to you, and you take a lot of pride in your work.

So with this I'd like to say thank you to everyone, and I'll be happy to take any questions if there are any. If not--

MR. NORTHRUP: I'm Steve Northrup with Medical Device Manufacturers Association. We spent a long time talking today about the re-engineering of CDRH, and they've been doing a tremendous job, and the need to overlay some of

that on what CBER is doing. Is the Device Action team giving any consideration to transferring primary responsibilities for device review from CBER to CDRH?

DR. ZOON: At this time the answer to that is no.

MR. NORTHRUP: Any particular reason why that's not on the table?

DR. ZOON: I think the Device Action Plan was really geared toward looking at what CBER's responsibilities are, and I think while that possibility might exist, I think it also reflects very much on the comments made today. I think if you look at the standards by which devices are reviewed and the appropriateness of the standards and their application, the consistency and transparency, organizationally it doesn't matter where they're reviewed. It's what the processes and procedures and performance are. And some of the issues with respect to blood as pointed out today, which many of our devices are, have some very unique properties that are very much different from what is regulated by CDRH, and their close relationship to blood safety is of a major paramount public health importance. And we cannot overlook that in any plan that we generate. And it's relationship, especially in the blood area, is very, very close.

For those of you over the years that have been intimately connected with this, we have competing forces in

the blood area. We have some forces from the public that say everything needs to be safer, safer, safer, and more and more oversight, and a competing force saying that we need products out there faster and more available. So we have to really come on a knife point on where we are with respect to the regulation of these products, because the balance doesn't give us a lot of flexibility on either side.

And quite frankly, the importance to blood safety and as it applies to tissue safety, et cetera, is even more key as new products from cellular therapies are generated, looking at stem cells as Paul McCurdy mentioned today, the core blood cell issue, I just think there's going to be more and more public scrutiny over this, and to a large degree if FDA doesn't do a good job many of these new technologies could be undermined, because they'll lose public confidence.

So I think we need to be careful in balancing all these competing forces, and be receptive to what the needs are of the different constituents and try to do the best job we can. But I think it's not quite as simple as just saying here, CDRH, you do it. It's a good question, you got a response.

Carolyn?

MS. JONES: Dr. Zoon, just a question of the team that submitted together the Device Action Plan. With CDRH did you find it beneficial to have industry involved in the

upfront development of some of those plans? Is there a possibility to get industry representation on the team or some sort of organized way to get their input? I mean before we put the plan out --

DR. ZOON: I think there are several aspects. Certainly this meeting is a beginning of trying to get the input into that plan. My sense is one of the areas and one of the things that we had done for those of you who might reflect on the tissue strategy was actually put out the tissue strategy for comment, and while -- again there's two levels here. We don't want to drag this thing out ad infinitum, but it may be that we can get as much input now, get started and I think Dr. Donlon reflected some of my personal views, that I'd like to be able in the first year of the action plan -- and where's Emily, Emily made some comment, the skinny rabbit. To really get something done and do it well, and show products from the fruits of our labor from the Device Action Plan, and really make some significant accomplishments. And I think that's important to us, and it's important I think to our customers.

So I see this probably as a multi-year plan for us, but I think we will be very happy to here what people think are the priorities as we implement our plan, because we won't be -- my concern is if we try to fix everything all at once we aren't going to fix anything. And we will dilute

ourselves to the point where I think we won't be affected.

So my issue is to really look at it on a priority basis and also looking at what we can accomplish realistically in a timely way and moving forward with that, but keeping the priorities of those stakeholders in mind in our first actions.

So we really appreciate that.

I want to thank everyone, and enjoy the rest of the day and thank you for coming.

(Whereupon, at 1:52 p.m., the meeting was concluded.)