FDAMA STAKEHOLDERS MEETING

APRIL 28, 1999
Boston, Massachusetts

Talking with Stakeholders About FDA Modernization

Boston University Medical School
Keefer Auditorium
715 Albany Street
Boston, Massachusetts
10:00 a.m. - 4:15 p.m.

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I N D E X

PROCEEDINGS

MS. FAIRFIELD: Good morning. Why don't we get started. We're running a little bit behind, and we'll get started and try and keep this on track. My name is Paula Fairfield. I'm with the Food and Drug Administration, and I'm just going to give you some housekeeping information. Rest rooms are just outside the door to the auditorium. They will be on your right.

We're going to have a break after our third speaker this morning from Genzyme Corporation, and the break will be in the Wilkins Boardroom, which is just down the hall on your left. It's across the hall from the clock on the wall.

Lunch is going to be in the vicinity of 11:45, and that's going to be on the 14th floor here in the medical center, and there will be signs and people directing you to elevators and around up to the 14th floor.

I would like to introduce at this time our District Director at FDA, John Marzilli, from the New England District Office. John?

MR. MARZILLI: Thank you very much, Paula, and thank you, everyone, for getting here this

morning. I know if any of you came in on the Mass. Pike -- and I came in on the Weston toll link -- then I can assure you that people are crawling along to get here. Normally I travel to our office up in Stoneham, Massachusetts, and don't experience the delight of Mass. Pike morning traffic coming into downtown Boston, so it was a novel experience for me, and I'm sure I'll do as the director of security here did and get here at 6:00 o'clock and have some coffee so I won't have to be pulling my hair out as I'm driving along the Pike.

But I want to thank folks for coming here, and I can assure you, as the day progresses, bit by bit you'll see these seats fill up because we have over a hundred people registered for this meeting, and it shows the tremendous interest in the New England area of people from the biotech industries in getting a chance to meet with us at the Food and Drug Administration.

This is truly a historic meeting for the Food and Drug Administration. We are having this meeting today as an outreach with our stakeholders across the country. The meeting

kicks off here in Boston this morning at 9:30 with the first of eight meetings that will be held across the country. Our meeting will start with the morning session with folks from the District Office and folks from the Center for Biologics. The day will progress where we'll have speakers from industry addressing us as well, folks that we're near and dear with that we've had working relationships for a long time here in the New England District, and are always first and foremost to come forward and meet with the agency, and we look forward to that opportunity.

It's an important aspect of the FDA Modernization Act for us to get together and hear from our stakeholders, hear from the people that we work with on a daily basis, and have a chance to interact and maybe, to paraphrase Ed Cox, to get a chance to say, "So how are we doing?" and see where there's room for improvement and room where we can work together.

It's an important opportunity for us as an agency, something that we don't get to do very often and something that this Commissioner has

highlighted as her first priority in taking over the reins of the agency that she came on board. So the FDA Modernization Act is Commissioner Henney's, and I can assure you my, first priority as District Director here in the New England District, and it's important for us to take this opportunity to meet with all of you.

As I said, there are seven other meetings being conducted across the country. In Atlanta we'll be having a stakeholders meeting with the Office of Regulatory Affairs. They will also be meeting in Chicago with the food industry. They will be meeting in Kansas City with the veterinary drug industry; in the San Diego area, medical devices. In San Francisco we'll be meeting with the biologics industry as well; and in Philadelphia, we'll be meeting with the Center for Drug Evaluation.

And, Paula, have I covered all the meetings? And if I haven't -- oh, in D.C. we'll be meeting with the world. Thank you.

And I'm sure all of you have clicked onto our Web site and seen where these meetings will be held. And for those of you that have fellow

workers that maybe couldn't make it to this meeting, at the break you may want to call them and tell them they can click onto their computers on www.fda.gov, and click onto our FDAMA Web site and see the Commissioner's broadcast simultaneously on our Web site as well. So we'll have a satellite broadcast that will be received at eight locations across the country with FDA participants. There will be other locations that will be receiving the satellite downlink as well, and people can also view it on their Web sites in their offices.

This is a first for me as District Director, and it's an exciting opportunity to take part in this activity as it goes across the country and get to meet with folks from the New England area from the industry that we regulate here, and I'm really looking forward to spending the day together with all of you.

And I would like to thank Boston University Medical Campus for hosting this meeting with us today. It was encouraging to work with them, and they have been the greatest of assistance to us in putting this together. And I'd like to

welcome Dr. Aram Chobanian, the Provost of the Boston University Medical Campus and the Dean of the School of Medicine. I'd like to ask him to come up here and welcome us to the site today.

DR. CHOBANIAN: Thank you very much, John. It's a pleasure to have you all here today. I go back with the FDA for a long time, for twenty-two years served as a consultant to the FDA, chaired the Cardiorenal Advisory Committee, and was on the Orphan Drug Committee for quite a while, so I feel particularly close to the group that we are sponsoring today.

Boston University Medical School and Boston University Medical Center is made up of different constituents here. At the medical campus we have four institutions, three schools and a merged hospital. The three schools are the School of Medicine, the School of Dentistry, and the School of Public Health. In addition, as those of you who are living in the Boston area know, we have a hospital that is a merged entity that brought together Boston City Hospital with our University Hospital; and that merger has gone very well, and we really have now a very unified medical

campus.

There is a lot of research activity here on the campus. The total sponsored program activity, if you include the school and the hospital, exceeds $150 million this year; and it's a broad range of research projects, some of which are working with your companies, actually. We range from the very fundamental work, molecular genetics, all the way to translational medicine, to studying devices in the animal care facility, and to evaluating clinical instrumentation as well.

There are thirteen nationally designated Centers of Excellence, most of which are funded by the NIH, some by other agencies, and those included a wide range of activities. We have a specialized center of research in hypertension, in coronary heart disease, in Parkinson's disease and Alzheimer's disease, in asthma, in chronic pulmonary disease, in mass spectroscopy, where we competed successfully for the National Mass Spec Center, which collaborates now with people both in academia around the country as well as with industry.

We have a Navel Blood Research Laboratory that's been very successful, and I know some of the individuals here have worked with Bob Valleri in that kind of setting. We have a Center of Excellence in Women's Health and so forth.

The exciting part of what we're doing right now that I think relates to some of your activities is the BioSquare enterprise, which some of you probably parked really in the middle of that nine-acre complex, and we have a master plan that's been approved that includes six buildings. The first two buildings you see, the second of the two, the Evans Medical Research Building, will be completed in December or January; and about forty percent of that building is for commercial purposes, for biomedical research for biotech companies. And we have a third and fourth research building that has been approved by the Master Planning Group. A garage is going to be started in the summer, and a hotel is currently being planned, and there are some preliminary discussions with companies regarding that.

In addition, our hospital here has a very

active plan. Many of the old buildings, Boston City Hospital, will be demolished this year, and a new ambulatory care facility that fits into the style of the other older buildings that are here will be constructed, probably beginning this fall. So I think we're seeing a major change here in the whole area, and it's going also with the changes in the residential part of this area, which is including now a large number of brown-stone conversions to condominiums. And I can't believe the prices that these condominiums are now going for. You could have increased the value fifty-fold. When I first came here, they were selling for between $5,000 and $10,000, and now they are about a half a million dollars.

So thank you all for coming. We really appreciate the opportunity to host this and hope you have a good day.

MR. MARZILLI: Dr. Chobanian, I'd like to pronounce your name correctly, having my name so often incorrectly pronounced. Dr. Chobanian, I want to thank you and I want to thank your staff for the wonderful job they have done for all the logistics for this meeting. It's just been

really great. We really want to thank you and extend our thanks on behalf of the Food and Drug Administration for all the assistance you've given us. Thank you very much.

And now I'd like to introduce Paula Fairfield, our Public Affairs Specialist, and Paula will tell us a bit about the logistics for this morning.

MS. FAIRFIELD: Thank you, John. We're going to have presentations from the Deputy Director for the Center for Biologics Evaluation and Research, Mark Elengold. Seated to Mark's left is Steve Masielo, who is the Director of the Office of Compliance at CEBER.

I'd like to ask the first three speakers if they'd come up to the stage, please. We're going to have presentations by Janice Bourque, Executive Director of the Mass. Biotech Council, James Weston, Vice President, Government Affairs and Strategic Policy at Biopure, and Lisa Raines, Senior Vice President from Genzyme Corporation.

After their presentations, we'll have a short break. Then we'll continue with three more presentations. Alison Taunton-Rigby, President

and CEO of the Aquila Biopharmaceuticals, Lisa Lopez, Corporate Vice President and General Counsel of Haemonetics Corporation, and Carolyn Jones representing HIMA.

When the presentations are finished, we'll have a period of questions and answers, and then we'll have our lunch break, which will be up on the 14th floor. At 1:00 o'clock the satellite downlink presentation will begin.

If you look in your packets, you'll notice on the left-hand side behind the agenda is a form, FDAMA Stakeholders Meeting. If you'd fill that out with the questions that you'd like faxed to headquarters, we'll have people that will take them from you and fax them directly.

Before the day is over, I'd like you to complete the evaluation for the FDA video teleconference and leave that with one of our people out at the registration desk.

On that note, I'll turn the meeting over to Mark Elengold.

MR. MARZILLI: Mark, I just had to make a couple of announcements.

MS. FAIRFIELD: What did I forget?

MR. MARZILLI: No, no, I forgot. You know, to err is human, since I made the mistake, right?

First of all, is Michael Donovan still in the house? I think he just walked out. I meant to introduce him earlier but I didn't get a chance earlier, so later I'd like to ask Michael to come down because he was a great help to us in putting all this together.

And, lastly, at the rear door there I'd like the two ladies to step forward so I can introduce them. In case you have any questions during the day and you ask me, I will flag one of them down to get the answer. And I want to introduce on our left is Karen Archdeacon. Karen is a Compliance Officer with the District Office. And on our right is Ellen Madigan. Ellen is a commissioned officer, and she is a biotech expert in our Investigations Branch. So I can assure you any questions you have for me, I'll be waving to one of them to come down so I'll be sure to get you all the right answer.

MS. FAIRFIELD: John and I make a good team. What I forget, he picks up.

MR. MARZILLI: Thanks a lot. And now Mark. And if Michael reappears, I will ask him to come down and introduce himself because he was a great help to us.

And here's the introduction. Let's have a drum roll, ladies and gentlemen, for Michael Donovan. Mike, come on down.

(Applause.)

MR. MARZILLI: I'd like Mike to introduce himself and tell us a little bit about the operation here because he was a great help to us in putting the meeting together.

MR. DONOVAN: Welcome. My remarks are going to be very brief. I'm not going to go over what Aram has already described in terms of what's happening around here. We're delighted to have this group here today. I work on the BioSquare project with Kathy Doyle who's up there on the right with Thompson, Doyle, Hennessey & Everest. And we're seeing, I think, unprecedented growth going on in this area. This is a part of Boston that is probably the next frontier, I think, for development in commercial activity. And today throughout the day I'll be around and Kathy will

be around. You'll probably see some information regarding BioSquare. If any of you who are from companies or, frankly, for that matter, from the FDA, if you'd like to find out more about what we're doing here, just feel free to talk to me or talk to Kathy, and we'd be glad to answer your questions and give you a tour or presentation later on. Thank you. Welcome again.

MR. MARZILLI: And now, since I so rudely interrupted, Mark Elengold. Mark?

MR. ELENGOLD: Thank you, John. It's a real pleasure to be here. I always enjoy getting out of Washington. I transferred there twenty-seven years ago for a two-year assignment, and I have been trying to get back out to the field ever since, so the closest I get are meetings like this.

I really want to thank everybody involved in putting this together: Dr. Chobanian for making this facility available, the folks at Mass. Medic and the Mass. Biotech Council for their support, particularly to Paula and John, folks back in headquarters who did a lot of the work on it, Lorrie Harrison, some of the other staff in our

Office Communications Training Manufacturers Assistance.

And the first thing I'd like to do is just introduce some of the other headquarters people that are here so you know who they are and you don't say anything to them that you might be embarrassed about. John's already introduced Steve Masielo, who is the Director of our Office of Compliance and Biologics Quality. That is a relatively new office that was formed by joining our staff from the licensing products surveillance people with our compliance folks to make a more unified approach to product quality and show how important that is to the compliance effort.

Gail Sherman right here in front, who's with the Division of Manufacturers Assistance and Training, a division that in my former job I created to give more emphasis to the fact that we have to assist manufacturers even if we don't have it in our statutory books that license do. Gail's staff is the one that works in doing outreach programs, and John and I have been discussing various things we can do to work more

closely with New England folks. And so if you have any ideas or needs, the person to talk to is Gail and to John and Paula. We'll be back, and we will continue our working relationship after this meeting.

Also we have Bob Miller from our budget office. Bob is the one who's responsible for making sure I have the money to pay for plane fares to come up here. And Bob, if you have anything you want to talk about the FDA budget, he's the guy to talk to. I was at a conference call the other day and they referred to him as "Bob show-me-the-money Miller." I've known Bob a long time, and I'd never heard that one before.

So that out of the way, let me explain why we're -- how many people were at any of the 406(B) meetings last year? Very few, so I'll go over this.

Part of the Food and Drug Modernization Act, a process that in the creation and birthing of was probably rougher than raising my twins for twenty-one years, one of the steps was that we would meet with our stakeholders, the people who

are affected by what we do, and consult with them on what the priorities are. Last year we set up very quickly a series of meetings to do that, and if anyone doubts that they had a profound effect on the way FDA does business, they'd be wrong. We heard the message loud and clear from the device folks that we regulate in CBER, and today we'll be talking about our Device Action Plan, which is a direct outgrowth of what we heard last year at the two 406(B) meetings that we had, and another industry exchange meeting that was held with the Pacific region folks that is directly attributable to that.

The way we did this last year was, we had it on different days for different centers, and most of them were in Washington. We in CBER had a second meeting in addition to the Washington one in Oakland, California. We believe that the meetings are so important for us to learn that, once again, we're the only center that's having two. I'm chairing this one here, and Dr. Zinner, our Center Director, is chairing one in San Francisco later today. The difference is that this year we're doing them simultaneously

featuring a video teleconference with Dr. Henney, our new Commissioner. We say "new," but she's had a stint as the Deputy Commissioner for Operations where she was in charge of the day-to-day operations of FDA, including the operations of the Center, so Dr. Henney is not a newcomer to FDA.

Part of that whole process is to have questions answered from around the country, so again I remind you what Paula said about this ivory-colored form. And, please, if you have any questions you'd like addressed, put them in, give them to the folks in the back, and they'll get them faxed to the teleconference.

Any questions that are not addressed during the course of the teleconference, we will have answered. We'll aggregate them. They will be answered, and they will be posted on the Web site within a few weeks. So even if we don't get to your question during the telecast, we will try to address all the questions and concerns.

The way we did this last year, and I think we'll do it this year, is I'll do a hopefully brief overview of what CBER is and the directions

we're moving in. Then we'll go to the panelists, and what I'd like to do is have them do their presentations. I think this group is doing it as one, if I'm correct. So after they conclude their presentation, my FDA colleagues and I will ask any questions we have on their presentation. Then we will open it up to the floor if anybody on the floor wants to have any comments or put questions to the group. After the first panel, we'll take a break, and we'll repeat that with the second panel, with the exception that we'll probably go to questions and comments after each speaker. Then we'll have lunch upstairs. Then we'll come back for the teleconference. After the teleconference, if we have not finished any general questions, people who have not registered, speakers who want to talk, we'll do at the end. Otherwise we'll just wrap up and adjourn.

Again I'll ask you to complete the evaluation forms because the statute says we'll do this at least once a year, and anything you can give us feedback on to help us will be appreciated.

Okay, let's see, I think I've got all of my administrative notes done, and I guess we can start with the slides. Again I want to thank BU and the audiovisual folks. This is an amazing facility.

This is our mission statement, and those of you who were at this meeting last year, one of the comments we received was that in our mission statement, we didn't properly address the medical devices we regulate. So we're in the process right now of going through the internal administrative measure of revising our mission statement. And over on the right side of that slide you see we're adding "and devices." That shows we have learned, we have listened, and our commitment.

These are the spectrum of products we regulate. We used to do this as a rainbow, but we kept adding products to it and the rainbow wasn't big enough, so we went to the circle, which kind of illustrates that our products are related and do tend to flow from one to the other. Again you'll notice down at the lower left corner, we've inserted between Tissues and

Whole Blood "Medical Devices," again recognition of what we've heard.

These are the tools we use to both enter the Olympics and do our job. They are interlocking systems we have of review, research, surveillance, policy, and compliance. We have an attitude that compliance is the last resort. We would rather work through negotiation; but if we reach a point where that's not possible, we have the full tools of both the Food, Drug and Cosmetic Act and the Public Health Service Act to take regulatory action.

These are our vision statements. They are in your handouts, so I'm not going to spend too much time. It just reflects the history of the biologics regulatory scheme that was started actually before the Food and Drug Act, and the Center for Biologics was originally the Division of Biologic Standards of the National Institutes of Health. It was transferred to FDA in 1972, and then added the tools of the FD & C Act. And if you see the last statement is the most important, that our regulatory mission is our guiding principle.

What are our strategic goals? Well, the first goal, a high-quality regulatory process which is managed and integrated from discovery through postmarketing. We want it to be seamless from the day that product is identified in a lab, put in clinical trials, hopefully licensed or approved, depending on the type of product, and then postmarketing surveillance.

A high quality research program which contributes directly to the regulatory mission. Over the years that has been misunderstood. Our research is directly aimed at our core regulatory mission. To give you an idea of this, very recently a magazine alleged that an illegal vaccine was manufactured with an illegal adjuvant, squalene. I was able to go to our lab director, and within a week they were able to develop a new method, previously unexisting, to quickly screen for this illegal ingredient down to parts per billion. And we had to be able to have the research tools available. I can't even pronounce many of them, but we have multi-toff MNR. This was using electro-spray ionizing MNR. And they tried four or five methods they came up

with in a week. They totally validated it, and we're now able to run the regulatory samples. Without that research base, we would still be trying to disprove this allegation. So that's the need for our research program.

A high quality diverse work force, interactive information systems, and leveraging resources. That's where we go out and partner because Bob won't give us enough money to do exactly what we need to do. Okay, Bob.

Okay, what are our priorities? Well, Dr. Henney will be talking about her priorities during the teleconference, and our priorities are pretty much the same. Number one, implement FDA reform. Just last week we published in the Federal Register a required notice under FDAMA adopting specific CDRH guidances, and that was a milestone we were required to do and we met.

We have to meet or exceed the PDUFA FY99 performance standards. Just in case anybody doesn't know the acronym, Prescription Drug User Fee Act.

Take whatever actions are necessary to assure the safety of and public confidence in the

nation's blood supply. Right now, approximately what percentage, Steve? 50 some percent of the blood supply is under consent decree? 60 some, okay. That shows that a few years ago, we realized the industry was not about to voluntarily comply, so we now have court-imposed sanctions and review of what they are doing. Again, that was a last resort after voluntary measures failed.

Facilitate the development and approval of significant vaccine, blood and therapeutic products. Just again going back to the history of our center, the person who was the first Director after it came in, Hank Myer, and his then Deputy, Paul Parkman, were the actual developers of the German measles, the rubella vaccine. So we have a proud history of working to actually develop the therapeutics and work with the industry and the National Institutes of Health where we are located to assure that the development process is as quick and seamless.

And pursue excellence in research that is directly targeted to the evaluation of regulation, and I've already covered that, I

hope.

Improve our automated system support. You can't do anything today without computers. I don't think any of us would like to go back to the era before e-mail, automated data systems, and tracking of our things. Well, some of us might want to, but when I get home tonight and I have 140 for being out of the office for 24 hours, I don't know.

And continue to support efforts for a high quality, diverse work force.

This gives you an idea of what we're up against. If you look over here, the Prescription Drug User Fee Act has really been a two-edge sword for us. It provided additive resources to the FDA to speed the approval of covered products. One of the requirements of PDUFA, however, is that we maintain a base level of appropriated resources, that if we don't continue to spend, we don't receive the user fees. And over the past few years, as our budget overall has been flat-lined -- and a flat-line budget involves a basic decrease because of increased salaries and costs -- the share of what we've had

available for the other products we regulate is this little blue dot down there. So when people ask why we're not doing as much as we could in the medical device area, it's because to keep this area here, we have to spend our appropriated funds and take it from somewhere. You can also see that this IAG CRADA has been constant or increasing, and that's because we've turned to leveraging and working with outside organizations, getting grants from research institutions, interagency agreements with NIH and NIST to try and fund some of our product characterization and regulatory development by partnering with either early phase industry or the NIH or NIST.

Interestingly enough, you can see that our workload has been in the IND, or investigational new drug area. In our case, it's really investigational biologics. And you can see that the level, aside from a dip for a few years -- and if you plot the stocks of biotech companies, those of you in the industry know that that pretty much tracks declines in the biotech stocks -- has been increasing again. And,

importantly, the percentage of biotech is really up there.

These are numbers which are interesting. It shows that while many of the products are coming in as INDs, very few are leading to actual applications. That's the next phase of product development, and we're gearing up to handle as they move from research into licensure.

User fee performance, you can see we're up there at a hundred percent. We've met all our goals, and we are going to continue to meet them.

That's a really horrible slide. I can't read it from here. This just shows our review performance in numbers and percentages, and again you have those in your packets.

And one of Dr. Henney's key priorities is improving FDA in general, and our goal is to improve CBER's science base. Again, we have a proud history of research. Our predecessors have worked with Dr. Salk and Sabin on the original vaccines. Again, the people who are our management back when I first joined the center developed the rubella vaccine. And over the past

few years our science base has eroded, and we are now in the process of rebuilding it because it is necessary to make good and fast regulatory judgments.

And these are the goals we've set for ourselves in science: To realize the mission of bringing products of new technology to the market rapidly while ensuring their safety and efficacy. Nobody benefits from rapid approval of an ineffective or unsafe product, not even the sponsor, because the long-term costs of having a bad product out there are not even available to them.

And to realize the mission of reducing risks associated with products. I'm getting ready for a hearing tomorrow in the House, and one of the things we have to stress is: There is no medical decision that is ever made that is not a risk/benefit judgment. And it's very important that both the products are approved when that judgment in general is on the benefit side, and the prescribers, or users, have the information they need to make the correct evaluation.

And these are the strategies: Research,

standards development. Again, standards development is very heavily interactive with the industry. Surveillance, outreach, meetings like this, and premarket review.

Training scientifically, these seminars, and enhancing our databases. The meetings and seminars is a key point because traditionally in the federal government, when you start running short on cash, the first thing you do is you reduce travel because travel is extremely expensive and you can't demonstrate a return on investment. That is one of the things that's eroded our science base. If our scientists can't get out to meetings, present their results and consult with colleagues, they are not at state of the art. And so one of our goals is to increase our folks' participation in major scientific meetings.

Professional development, many of our physicians have for a long time worked in clinics, mainly free clinics or volunteer clinics, a few hours a week to keep their medical skills and patient treatment ideas up to the standard. We're enhancing that by getting some

of our research types, our microbiologists, our chemists, working in research laboratories in universities part-time, four hours every two weeks, to get some experience on what the real world is in today's day and age.

Product testing, we are in the process of developing a new standards group within the center.

And infrastructure, for many years our lab equipment was getting very old. It wasn't up at state of the art. One of the few benefits of Y2K means that some of that equipment has to be replaced just so it will work next year.

And I think I've covered those in previous slides. The key one I'll just repeat: Anticipate public health needs and support informed decisions. And that way, when we have our traditional Friday night crisis and my pager goes off at 9:00 o'clock and my wife starts yelling about the FDA, I can pick up the phone and get the people I need who can give the information that is needed to make the right public health choice.

And I think I've covered those. We'll just

shoot through those. You can read them.

Major initiatives of action plans: Two years ago we were faced with the crisis of confidence in the blood supply, and we developed the Blood Action Plan. And by putting resources and project management to it, we have been able to move a lot of things forward very fast.

It has been so successful that we have adopted the action plan approach for several things: FDAMA/PDUFA II. We have accountability. We have meetings. In fact, unfortunately I left yesterday to come here and missed our quarterly Status of Application meetings, where each of our review officers gets up and gives the status of all the applications they are working on; and the senior management can listen, provide input, and make assignments of additional resources or whatever is needed.

Strategic Plan, we developed that four years ago to give us a basic ten-year strategy. It has been very successful in anticipating both our budget problems and what we need to do to focus.

Team Biologics, I'm sure there will be some questions about that. That was a way to bring

our inspection compliance activities into line with the rest of the FDA. Twenty-five years after biologics was absorbed in FDA, we still did business in a major different way. Our inspection program was conducted out of headquarters, and some believed our GMP attitudes and compliance activities were out of line.

We believe that because of the cutting edge of our technology, our scientists really needed to be involved in the inspectional approach. So ORA and CBER got together, and we developed Team Biologics. I'll go over it in a couple of minutes.

Tissue Regulatory Framework, that's an action plan that's developing strategies to regulate tissues. Congress has for years been talking about enacting statutes. They have not yet done so, and we anticipate should it be done, it will be another unfunded mandate, so we have been working on how to come to grips with the tissue issues without any additional funding or resources.

The Blood Action Plan I mentioned was the granddaddy of the Xenotransplant Action Plan.

That came to light with Jeff Getty and his baboon blood marrow implant a few years ago. We decided we needed to get together and be proactive. There are companies developing human-gene-based pig organs. Our own research lab discovered porcine endogenous retrovirus, or PER, that's genetic codes from viruses that were embedded in porcine tissue. And we had some INDs for liver assist devices, and when this was discovered, our lab was able to do the research, find out they were nonreproducing, nonreplicating, noninfectious, and therefore didn't pose a risk. The hold was very minimal, but we were able to investigate it, reach an informed decision, change the informed consent, and move on. Again, the need for a research program.

The Device Action Plan, we'll go into detail on that, and the ICH, so that the industry has a single group of requirements to comply with around the world.

Device Action Plan, in part spurred by the device law changes included in FDAMA. And last year we heard -- I heard it in Oakland, in D.C., and then again in Irvine. We had a meeting back

in December to discuss this in Bethesda. And what industry has said we don't provide is consistency, harmonization with CDRH, a transparent process they can understand, facilitated reviews, guidance, and communication.

So we have set up four teams as part of the Action Plan: CBER/CDRH Coordination, Review Performance, Compliance and Team Biologics, which I'm the chair of, and the Outreach/Inreach, which Mary Myers, who is the director of our Office of Communications Training Manufacturers Assistance, is in charge of. And that is designed to both get our message and hear the messages of our stakeholders in the device area, as well as deal with our own employees who may not understand what's going on. That's why we added the inreach to the always traditional outreach.

Coordination has a bunch of action items. The Intercenter Agreements are now many, many years old. Aside from my gray hair, my memories of the original Intercenter Agreements and implementing the '76 drug amendments reminds me just how old I am. We realize that technologies

and products have come down the pipeline that weren't even thought of or imagined at the time of those agreements, so we are working with CDRH and, as a matter of fact, CDER, but we're starting with the CBER/CDRH agreement.

A Re-engineering Work Group that was so successfully set up by Bruce Burlington, we're working with them to get their lessons learned so that we don't reinvent the wheel.

We've published the FR Notice of Concurrence. I think it was last Friday.

FDAMA training at CDRH, our people are attending the training that CDRH reviewers get, and in fact, on some products the CDRH reviewers are attending our training.

Device Web page, if you look at our Web site, you now have the devices separately, so you don't have to go hunting through the material, again a direct outgrowth of last year's 406(B) meetings. And we are preparing guidances on many, many issues relating to medical devices.

The CBER/CDRH Coordination Outcomes, Commitment: The commitment to review devices in a timely manner using the same standards as

CDRH. Coordination with them, cooperation, communication, and again consistency. I believe those of you who were at the meeting last year can testify that that is exactly what we heard.

Review Performance, our review performance in the device area is, quite frankly, very poor. We realize that, and it's a result of funding. The same people who do that have been involved in providing the scientific support of those injunctions on 60 percent of the nation's blood supply. Compliance issues have to come first, and as you saw in that one slide, we keep reducing the amount available to other products. We have a proposed reorganization in our Office of Blood, and that will hopefully give more attention and control.

Set Review Objectives, Implement Managed Review Process. We developed a managed review process to implement FDAMA and PDUFA. We are extending that to include the blood process. That is where we mapped out our business rules. They covered three walls. We're now looking to where we can re-engineer that. We have something called the 2-B process that we're working on, and

that is almost finalized. When it is, it will be up on our Web site.

And Develop Targeted Guidance for specific products in specific areas.

Review Performance, again closely managed process, define expectations and priorities, meet time frames and deadlines, and maintain the review quality. Again, no one benefits from a poor product getting approved.

Compliance and Team Biologics, as I said, I chair that group.

Review the device inspection policies, make sure they are conforming with the CDRH policies, except where the nature of the risk from the product justifies an exception. We will not be lowering standards, but we will identify the ones where we can and evaluate that, and where they are different, we're going to clearly explain them, both to our own people and to the industry, as well as why.

Training and guidance, we will be training our own people, and we will be doing what we've done traditionally in CBER, and after developing the training program, hold a similar program

available to industry so they can hear the same words the investigators hear.

Develop sterility and stability, I guess the word got left off there, guidance for the inspectional program, and GMP guidance for CBER IVDs. That is an issue that came up frequently last year, and we have a group that's composed of CDRH, CBER and ORA, our field people, that will be coming up with an explanation of what the standards are, and if they are different, why.

ORA coordination, a transparent inspectional process, just one that when our investigator walks in, whether it's a district investigator or Team Biologics team, you'll know what they are going to be doing.

And a consistent compliance approach. Over the years, we have heard that different districts do things differently. In fact, I've heard that for close to thirty years now. The way we're handling that in the biologics area is part of Team Biologics. We have two compliance officers, one on the East Coast, one on the West Coast, to coordinate our actions. So we have reduced the number of people to oversee it, and so we get a

consistent approach.

Outreach/inreach, developing strategies I talked about to explain what we'll be doing there, or actually what we are doing doing here.

The 21st Century Biologic Products, when I left the Center for Drugs and came over to Biologics about eleven years ago, I had a long conversation with my mother, who's my reality-based check, and she said, "What's the difference?" And I tried to explain to her that blood and vaccines and other biotech things like gene therapy, cellular therapy, monoclonal antibodies, and she had no idea what I was talking about. She has now learned by watching the evening news that every time she hears about one of these new products, she'll ask me, "Is that thing I saw yours?" I say, "Yes, that's ours."

It's clear that the future of biomedical science is in the biologics area. So what are we going to have to deal with? New biomedical technologies, the safety of those, ethical issues. I remember a happy time in my youth at FDA when we used to say ethics weren't really our

issue; that was the IRB's and the institutions themselves and the companies. That's not true anymore. We really do have to get involved, particularly things affecting the germ line, where the ethical issue is part of the benefit-to-risk equation. And the harmonization of regulatory standards, both within FDA, but more importantly, around the world.

Changing health care environment. I remember telling people, and telling people on the Hill particularly: "FDA doesn't get involved in economics. We deal with safety and effectiveness." In today's managed care environment, that is part of the risk/benefit equation. A technology that is incrementally better but costs a thousand times more, is it worth it? And when you get into these discussions, for those of us who started out as FDA investigators, or as they were called when I was, inspectors, life was easy. You dealt with rat pellets in flour. You dealt with unsafe, adulterated, or sub- or superpotent drugs. Now we're involved with incremental change: Is a product that's a thousand times more expensive,

that gives a person a one in one thousand chance at a better outcome, worth it? Well, if you're that one person, you think it is. And it's a really strange discussion that gets involved with how you make those decisions on whether the approval is worth the increased risk or increased cost. Again, we try and stay out of it.

Bioterrorism, two years ago I knew nothing about bioterrorism. Now I have a Top Secret clearance and I know more than I ever want to. That is an important part of today's life. The Department of Health and Human Services has been given a large amount of money to purchase a civilian stockpile of drugs, biologics, and devices for use in terrorism. We are involved in that and are advising the department, facilitating development in dealing with that, another thing that has been taking up enormous amount of resources, and I'll say this again for Bob's benefit, was not funded in this current year's budget. Hopefully next year we will get some, but it is a very important thing for the civilian stockpile as well as advising DOD on their actions.

Y2K Issues. You can't pick up the paper today without finding out that January 1, the whole world is going to collapse. I was reading my local paper, and somebody in my neighborhood I know for twenty years has turned into a raging survivalist. She has more generators, dried foods. You know, it reminds me, those of us old enough, back in the '60s and the '50s with the fallout shelters. Now, this is something I've known for twenty years and I think is fairly rational. And the hype given to this has reduced the confidence of the public. So we're very involved with working with our industry, working with the department. We have a Y2K working group. Those of you in industry will soon be getting a letter from us to submit what you have done with your Y2K preparedness. We have been working on a shortage plan, which in addition to our normal shortage operations, makes sure that the products that we regulate will be there. Again, another big job that is unfunded, and this one's our bottom line.

In closing, I don't want this to be the last time we communicate. In my last job, I was

pretty proud of the information systems that we set up. I always used to keep this slide for last because most of the people at meetings were Internet-challenged. But now just about everyone has access, and we have a fairly large Web site. That's the address. And if you have a question in general, you can e-mail it to that e-mail box, and someone from our Office Communications Training Manufacturers Assistance will either answer it or get it to the person who can answer it.

Questions for Stakeholders, this is the purpose of this meeting. This was in the Federal Register Notice, and this is what we've asked the speakers to address. And aside from being in the slides, they are on those question sheets as well:

"What actions do you propose the Agency take to expand our capability to incorporate state-of-the-art science into its risk/benefit decision making?

"What actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its

public health responsibilities throughout the product's life cycle?

"What actions do you propose for educating the public about the concept of balancing risks against the benefits in public health decision making?

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

And, "What actions do you propose for enhancing communications processes that allow for ongoing feedback and/or evaluation of our modernization efforts?"

And that's it for the slide talk. I'd be happy to answer any questions or you can save them for after the speakers. Anyone? That being said, I thank everybody for their patience in listening to me.

(Applause.)

And I want to thank the folks back at the office that put that one together. If any of you are interested in sharing these with colleagues -- I know some companies, I hear from people who have left the FDA, require you guys to

make out trip reports and things. These slides have been posted on our Web site since yesterday. So if you want them in color that you can attach to e-mails and stuff like that, you can just download it. They are in Powerpoint, and you can get the entire set if you want to do briefings within your own company.

The other thing is, as of yesterday, the Device Action Plan, which was signed by Dr. Henney last Friday, is posted there as well. It was only approved last Friday, and we didn't have enough time and we weren't real sure whether we would be able to get it out here. And if you are in that sector and you want to see the exact plan that follows the tracks of what I had up there but with the specific goals and the due dates, that's there.

Okay, our first panel, Janice Bourque, Executive Director Mass. Biotech Council; another friend from last year, Jim Weston from Biopure; and Lisa Raines from Genzyme, a very well-known company here in the Northeast. And there's Steve and John. And just go ahead. Do you want to come up here?

MS. BOURQUE: We're going to use the overhead.

Okay, well, thank you for allowing us to speak again today. As was mentioned, we were in Washington, D.C. last year, so welcome to Boston. We've also had a recent visit with Dr. Henney. She came and visited the Mass. Biotech Council and the Device Council as well, so we were pleased to have the opportunity to talk with her about some of our concerns and what some of her concerns are as well. And we have worked closely with the local FDA office, and I'll point out how well we have worked together on a pilot program that was very successful and has continued and ongoing.

Today we have, as I mentioned, three speakers, myself, Jim Weston, and Lisa Raines. And I'm going to talk a little bit about meeting performance time lines, FDA reviewer training, and advisory panels. Jim Weston is going to talk about risk/benefit and consumer education, and Lisa is going to speak about fast-track generic biologics and pediatric exclusivity extensions with regards to orphan biologics.

Just so you'll know a little bit about us at the Mass. Biotech Council, we represent about 250 companies here in Massachusetts. They are mainly small to medium size, and they range anywhere from early stage companies of anywhere from two to three people to full-scale commercial manufacturing companies with several thousands.

The MBC has been in operation for about fifteen years, and our primary mission is to ensure that all biotech companies, whether they choose to remain small or become fully integrated companies, reach their full potential.

Last year the MBC had put together an FDA White Paper in response to FDAMA and actually tried to come up with recommendations on how to actually carry out the implementation and write the regulation and have input into the guidance documents. It's one thing for Congress to write. It's another challenge, I think, for the FDA and for industry to work together to ensure that the regulations reflect that legislation and move forward. So we're very supportive of this mission to ensure that there's prompt approval of new drugs and therapies. And our primary goal

for the FDA, we know, and for the industry is to ensure that these patients have access to these therapies and that we're able to get them to them as quickly as possible.

One thing I'll mention today, we do have some copies of these slides. We will be submitting an actual document to the FDA. I think we have to about May 14, I think. And it will be similar to our White Paper. It will be a second White Paper with the actual text that will go into further detail from these slides, and that will be available. It will be up on our Web site as well as directly supplied to the FDA and to anyone who would like a copy of that.

For the first section on meeting the performance goals, I'd like to speak briefly about our last meeting. We had come up with recommendations in our White Paper regarding meeting performance goals, and since then a guidance document has been released. And in this guidance document we noted that we had made some recommendations on dispute resolution, and we had asked that the sponsor be able to provide corrections to the FDA fifteen days from receipt

of minutes from the FDA, and that in return the FDA provides response back to the sponsor fifteen days from receipt of the correction from the sponsor. We think it's very important that we have firm time lines within the guidance documents, and we believe those were not put in there. And that way the expectations are very clear from both sides just who has been operating within the response time that's necessary. I think to leave it open, again, leads us to a position where we are now where it's up for discussion, debate, and not necessarily being able to have a sense that we are moving the time line.

Secondly, with regards to meeting the performance goals, with regards to fast-track meetings and sponsor-requested fast-track meetings, we wanted those meetings to be scheduled within fourteen days of the request by the sponsor. And then we also requested that the meeting actually occur within thirty days of receipt of the sponsor's request, and that again was not noted or given firm time lines in the guidance document, and we're hoping that there's

still an opportunity to put those expectations in that guidance document.

With regards to FDA reviewer training, when Dr. Henney was here, she indicated there were three areas of great concern with her. One was actually carrying out FDAMA implementation. The second was on building the science base at the FDA, and the third was addressing real safety issues, and those were three of her primary focuses that she addressed to us.

So with regards to building on the science base, which I know some of the questions have been asked, the MBC, as I mentioned earlier, has a model program experience in the success area of manufacturing. With John's local office, we've been able to develop a preinspection pilot program, and that we actually won in conjunction with the local FDA office Al Gore's Hammer Award for a model program on helping to reinvent government and streamline it. So we have that expertise. So what we'd like to recommend is that we could develop a model program for FDA training.

Now, we know the reviewers already receive a

great degree of training, but we think that together with industry, we might be able to help develop that science base further. And so what we thought we could do is maybe create a seminar-type format in which cutting edge technology would be presented. And that could be presented by academia, by industry, leaders in this field of research that's going on who could present this type of cutting edge technology to allow the reviewers to come, ask questions, present the work they are doing.

It really creates a certain synergy. It's not for any one company or researcher to hope to gain an "in" with the FDA. This is really to talk about the science so the reviewers are right there. It's a challenge for us as an industry to stay up to date on all of the technology that's being developed, so we can only envision it's a real challenge for the reviewer as well.

I have a possible suggestion or solution. We could do it in a neutral location. We'd love to do it here in Massachusetts. There is a facility, the Mass. Biologics facility, which now comes under the purview of the University of

Massachusetts. There may be another facility as well that I'm not aware of. But the reason why I suggested this facility is because they already have conducted FDA training there, and it is a CDC alternative site, so we know they probably have the necessary equipment and the presentation rooms in order to do this.

And, similarly, seminars could be developed so that it's reciprocal between the FDA and industry. So if there are ways the industry has shortcomings in terms of its ability to interact or report or have discussions with the FDA, there are things that we continually do, ways that are ineffective, we certainly would welcome the FDA to also give seminars to us in how we can do that better. So we really see this as an interactive opportunity to develop a model program. And there may be some things similar. We certainly don't want to say this is just something associated with Biologics, but maybe this could be expanded to include products. I mean, whatever opportunities we see there.

The last point I'll make has to do with the advisory panels. In our earlier White Paper, we

did ask for harmonization between the two divisions. Currently CBER has what we believe is a great operating policy, where they actually submit to the sponsor their draft panel documents; and that allows a sponsor then to review and give comments back to the FDA before it goes back to the advisory panel. That's very important because let's say there was some point that was made incorrectly or confusion over a particular point. The sponsor has a chance to correct it before it's actually spent a great deal of time at the advisory panel going over something that simply could have been clarified ahead of time, so that when you're at the advisory panel meeting, you're really focusing on what is really crucial and important.

Right now CDER does not do that, rarely does that, and we would just really like to see CBER's policy harmonized and carried over into CDER. We think there's a real opportunity to use the advisory panel in the capacity that they were originally intended.

And with that in mind, also I want to talk briefly a little bit about the role at the

Advisory Panel. What we see the role of the Advisory Panel -- and I was looking at some of the documentation as to the description of the role of the Advisory Panel. It was really for a third-party evaluation mechanism for advice, particularly regarding scientific controversies or some cutting-edge technology that's really challenging. It is important that the FDA note the impact these Advisory Panel meetings has on the industry. They are open public meetings. They are often filled with a variety of individuals, including investors, and they greatly impact our ability to raise research dollars. And even if you get an approval from the Advisory Panel, we see fluctuations in stock, that even with a positive result, we'll see 20 or 30 percent fluctuation on the stock. So it's important to note that these panels, what they say and do has great impact.

But we're very concerned about how the panels are now being used. We think that perhaps they are used too frequently and they are used just to endorse what the FDA already used, not as third-party evaluators. And so what we'd like to

recommend is that if the company has proven safety and efficacy to the extent that the FDA feels is necessary, to maybe not go into an Advisory Panel review process, but go through just a rapid-approval process, and really use the Advisory Panel for controversial issues.

Additionally we also, because these are open public forums, we're asking that the FDA consider that these be closed forums, so that the discussion really does not affect the outside investors, the stock market or what not; that really instead of having individuals in the room who really don't necessarily need to be there, if it's going to be a scientific discussion, to really consider having closed Advisory Panel meetings. Certainly the FDA could have anyone there that they feel is important to be there, but limit who exactly ought to be in that room.

Essentially also we'd like to maybe have some conformity or best practices evaluated by the advisory panels. I think companies have various experiences on what worked well, how some advisory panels really operated, they felt, to both the benefit for the FDA and for the company,

as well as a third party and others that probably did not operate as well, and that there might be opportunities to develop conformity or best practices to address the Advisory Panel.

I'm going to have Jim Weston now come up and talk about consumer education and risk/benefit, and then we'll have Lisa. Then we'll take questions.

MR. WESTON: Thanks, Janice. As Mark Elengold mentioned, most products in the American marketplace really, especially medical ones, have two facets. On one side, we know that they really benefit users and often improve lives. We also know that they are, however, rarely without at least some risk, and that risk can result in known or unknown side effects. Consumers must often weigh the benefits and risks before using these products, oftentimes with incomplete information.

In order to address this issue, the FDA asked us for responses to the question: What actions do you propose for educating the public about the concept of balancing risks against benefits in the public health decision making?

We know that FDA's mission is to promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner. Under FDA's Plan for Statutory Compliance of last November, which addressed the requirements set in Section 406 of the FDAMA Act, several objectives were stated.

They included: Maximizing the availability and clarity of information for consumers and patients regarding new products, implementing inspections and postmarket monitoring, and ensuring FDA's access to scientific and technical expertise.

Let's talk a little bit about some of these. The ability to improve public education and understanding about the concepts of balancing risks against benefits in the public health decision-making process could be enhanced with several new and expanded concepts developed and implemented by FDA, sponsors, patient groups, and other governmental agencies. First, the concepts of risk/benefit analyses should be expanded in discussions and agreements between the FDA and

sponsors throughout the entire development process. FDAMA provided a guideline for the management of meetings between sponsors and the FDA and the MBC, the Mass. Biotech Council, in its July 18 White Paper provided points to consider relative to the meeting section of that document. In accordance with some of those proposals which we made and agreed upon, there should be during each critical meeting decisions and agreements made relative to risks as well as benefits. FDA should discuss the criteria development agreements that will form the basis of an acceptable risk as part of the overall approval and development process.

Furthermore, if a product is to be discussed at an Advisory Committee meeting as part of its approval process, a summary of both the FDA and sponsor agreements and opinions regarding the risks/benefits of the drug which have occurred in developing the development process should be presented as well for a balanced review.

Secondly, the agency's criteria for presenting well-balanced information to the consumer needs to incorporate all aspects of the

health care system. Risk/benefit information is provided in the package inserts which accompany distribution of most prescription products. It's also associated with ads for prescription products, and a patient package insert is often provided when a prescription product is dispensed. But because of the complex nature of this information and often the general lack of public knowledge regarding the development process, this information is often not read, is either overlooked or can be misinterpreted if at all read.

While other forms of communications are becoming available -- for example, on Web sites -- the same information is often provided in just a different manner. In order to address this concern, we would propose that FDA explore pilot programs with effective education regarding risks/benefits of prescription products, with the primary public contact persons giving out prescription medicines; that is, the prescribing physicians or dispensing pharmacists. These are the individuals with the background and training to understand the risks/benefits and who can

directly assure that patients best understand the risks and benefits of the products. This type of program would be extremely beneficial, particularly for fast-track products where there are often high risks involved.

The FDA does have a Pharmacist Education Outreach Program, and we encourage its expansion. In today's managed health care system, it's likely that insufficient time is allotted or allowed for this purpose. Thus a cooperative agreement must be reached between all parties in health care systems, the sponsors, the FDA, the physicians, the pharmacists, and often health care peers, to be able to provide this information in time to give benefit to patients.

Collaboration with all stakeholders -- i.e., the media, the consumers, the patient groups, and other federal agencies -- is encouraged.

Third, the timely dissemination of current and cutting-edge "scientifically sound" information regarding potentially new uses and findings of drugs and biologics should be expanded. This includes the dissemination of information on unapproved new uses and timely

information regarding postmarketing surveillance of new and existing products.

FDA and sponsors need to work cooperatively to develop the full potential of the Internet as a two-way communication tool as part of this process. Information regarding new approved and "scientifically sound" information on unapproved uses should be readily available to consumers and health care professionals in an effective manner. In a similar manner, safety profiles and updated safety information regarding products should also be available freely on the Internet. Information from FDA's Adverse Events Reporting System should also be promptly posted.

And, lastly, the FDA in order to communicate effectively with consumers and patients, needs to enhance and expand the agency's collaborations with industry, other governmental agencies, academia, and patient groups. In this manner, information exchange, scientific expertise, and important interchanges regarding key information, including risk/benefit analyses, can occur. We strongly encourage FDA to expand its interactions with the NIH, the National Institutes of Health,

regarding the science-based expertise and patient education process.

And Lisa Raines?

MS. RAINES: I didn't make advance arrangements for somebody to do my overheads, so Janice is being very kind to help me out here.

In the remaining time, I'm going to address three issues, each of which is fairly complex, and so each of which is going to be addressed in a fairly shorthand manner. And if there is a minute or two remaining, I may take the opportunity to offer some personal comments on some of the issues that Dr. Elengold raised that we've had some discussions on in the industry.

The first issue I'd like to talk about is the new Fast Track Program which we're very excited about, and in fact had the opportunity to discuss with Dr. Henney when she visited Genzyme for close to an hour just a few weeks ago. And let me begin by saying that the concept of fast track, which was developed in collaboration between FDA, the Congress, and the industry, was to look at best practices that FDA had already adopted through the Accelerated Approval Program,

or through what we sometimes call "skunk works," where individual reviewers had taken extraordinary initiative to move products through the pipeline in a rapid and effective way, and to see if we could come up with some way of institutionalizing and broadening the scope of what we viewed as best practices that FDA had already implemented.

I think to a significant extent we all recognize that fast track initially builds on the existing accelerated approval regulations. FDA put out the guidance document required by the statute a few months ago, and by and large, I think it's been very well received by the industry. It recognizes that fast-track products may either be accelerated approval products based on an approval on either a surrogate end point or a short-term clinical end point, or it may be a regular approval, and you've got the advantage of rule and review in either case. But I'm going to focus on the accelerated approval side because I think that the regular approval side is the area with which there's broadest experience and broadest knowledge, both on the part of the

industry and the agency, and at the accelerated approval side where there's still a lot of clarity that we think could be injected in the system.

As most of you probably know, in 1992, largely in response to the AIDS crisis, FDA adopted an accelerated approval regulation that recognized that the risk/benefit analysis with respect to a serious or life-threatening disease, for which there was an unmet medical need, required a greater degree of flexibility than another headache remedy. And so FDA developed a regulation under which they indicated that an accelerated approval could be provided in the absence of proof of effect on morbidity, irreversible morbidity or mortality, if an effect could be shown on a surrogate end point or a short-term clinical end point that was reasonably likely to predict clinical benefit.

This provision raises a couple of questions. Scientists sort of take as a given that a P value of less than .05 proves the validity of an end point in affecting morbidity or mortality; but when you talk about something

being reasonably likely, that's clearly less than proving validity. And so the question is: How much data do you need to prove that a particular chosen end point is reasonably likely to predict a clinical outcome? And we're not sure that there is consistency or clarity on this point.

If you look at the examples in the past, AIDS, I think, being a brilliant example, the one with which there's most experience and the most products and where the surrogate end point -- namely, CD4 cell counts -- has now been validated through showing increased life spans for people who take the products approved under this regime, there was evidence showing that a reduction in the immune system eventually led to people getting sicker and eventually dying. And so it was hypothesized that if you could increase that cell count and improve the immune system, that you could make people live longer. But that wasn't proven until long after people had actually gotten these drugs after they were approved, and really over the last year, where major scientific conferences have come to a consensus that the selected end points were

validated. But there was a good scientific basis for expecting that the correlation was so close between morbidity and a decline in the immune system, that an improvement in the immune system would in fact improve life span, and that's now proven to be the case.

But as we looked at other non-AIDS products and we look at noncancer products -- and AIDS and cancer are the two principal areas where accelerated approval has been used -- we found great more debate as to how much data you need to show that a particular chosen end point is reasonably likely to predict clinical benefit.

Now, remember, in the case of all of these accelerated approval products, there is a phase for postapproval study requirement, which essentially requires that the end point chosen be validated and that ultimate clinical benefit be proven. So the concept is that ultimately, yes, we do need to prove clinical outcome as approved by the product, but we can approve the product short of that and collect the full validating data on a postapproval basis. But how much short of that provides adequate confidence for FDA to

believe there's substantial evidence of safety and efficacy?

These are some questions that we would like to ask and we don't have an answer for. We believe that the industry and the agencies should be collaborating on a discussion of these questions, a discussion that I think has taken place on a very ad hoc basis product by product, but where there aren't general principles.

What the AIDS drug manufacturers were able to do, for example, was show an increase in CD4 cell counts but not an improvement in mortality. There are now some reviewers in CBER who believe that you must not only show an improvement in the chosen surrogate, but show the improvement all the way up to a normal stage, which was not required in the AIDS cases.

Remember also that these are for serious or life-threatening diseases where the drug has the potential to meet an unmet medical need. So we're not talking about having this greater flexibility except in those cases where there's a compelling case that it's needed.

The second question, which is a really

difficult one to grapple with, addresses: What do you do in the case of very, very rare diseases? My company, Genzyme, sells a product for one of the rarest diseases for which there is an FDA-approved product, serozyme. There are about a thousand U.S. patients. Serozyme is the most common of about 40 genetic disorders of the same type. There is very little data out there regarding the history and pathology of these other disorders. How is it possible then to develop reasonably reliable surrogate or short-term clinical end points when there's very little historical control data available, and where the patient population is so small that it's almost impossible to get statistically valid results even with a surrogate end point that everybody agrees is appropriate? You could do a clinical trial that requires every patient in the United States to enroll in the trial for some of these very rare diseases. How do you get there from here in a way that makes it possible for these products to be developed?

I want to just remark that FDA's fast track guidance document does discuss in a footnote the

use of short-term clinical end points to serve as the basis of an accelerated approval. There are reviewers in CBER who have said short-term clinical end points can serve as the basis of an accelerated approval.

So is this an education issue, or are we misunderstanding the type of short-term end points? There were some examples given that might serve as the basis of approval. And to what extent can we look at the previous and, I think, excellent FDA document that deals with the design of clinical trials to look for cross-confirmation of a surrogate end point and a short-term clinical end point that overall increases your confidence level but doesn't quite get you to the level of statistical significance, where there is a very small patient population in particular? And these are really the two points that I just mentioned, and they are in your handout.

I'm going to move now to the issue of generic biologics, and let me begin by saying that we were very pleased with Dr. Henney's response to the Senate indicating that she had no

plans to create a generic biologic approval system. And we were further encouraged when she was up here a few weeks ago and meeting with the MBC where she elaborated on that response and indicated that she believed that Congressional intent would need to be demonstrated before FDA would do that. And I think that's a wise approach to take.

I think aside from the fact that the 1994 amendments to the Food, Drug and Cosmetic Act don't address biologics and there's no legal basis for biologics to go through a generic approval process, there are some sound scientific reasons to look at these large complex macromolecules in a different way than the simpler molecules that tend to be the basis of most drug approvals.

However, we do have a concern with the fact that some products that most of us non-FDA staff think of as biologics, recombinant proteins, lipoproteins, are sometimes regulated as drugs. Some of these are products that predated the Intercenter Agreement in which CBER and CDER divvied up jurisdiction over these type of

products. Some of them have been assigned to one center or the other since then, and we're aware of disputes within the agency over which center would get to regulate a particular recombinant protein.

Those kinds of discussions, in our opinion, for scientific public health reasons as well as consistency and fairness reasons, should not create a result in which one product might go generic at some future point and the other wouldn't, merely based on the convenience of the agency.

The Intercenter Agreement, which was developed when there was a dispute over a particular product between the two agencies, is based on a very elegant concept, and this is a quote directly from the Intercenter Agreement. I'm sure the CBER people are very familiar with it, and on its face it seems that this concept is very simple: You basically put the product in whichever center it's appropriate to put it in based on its physical characteristics, source materials, or pharmacologic properties.

What we've seen, however, is that when you

actually try to apply these principles in combination with the historic jurisdictional interests of both centers, that you get some inconsistent results. And these are just a few examples that are real-life examples or that are specifically stated in the Intercenter Agreement.

For certain kinds of products, how you manufacture a product determines whether it is regulated as a drug or as a biologic. Polynucleotide products, for example, if they are made using recombinant DNA, are regulated as biologics. The exact same molecule, if it was extracted from tissue or chemically synthesized, would be regulated as a drug. And yet it may be for the exact same disease. It may have the same molecular weight. It may have the same composition. And the mere manufacturing method determines, is it a drug or is it a biologic?

On the other hand, there are other products for which the Intercenter Agreement says manufacturing method is irrelevant. If your product is a hormone, it gets regulated as a drug, and it doesn't matter if it's a recombinant

product or a chemically synthesized product. Similarly, vaccines and allergenic products are regulated as biologics with regard to how they are made.

So does manufacturing matter? The answer is: It depends on the kind of product. And I didn't see any clear scientific rationale for differentiating between these two classes of products and the general rule, except that historically CDER has always done hormones and antibiotics, and historically CBER has had authority over blood, and statutory authority at that. And so we had to carve out exceptions to our general principles to conform with historical jurisdiction, expertise, and other considerations.

Again, the source materials matter. If you take a product from blood, it's regulated by CDER. If you take it from tissue, which contains a lot of blood and which presumably has pretty much the same product, it's regulated as a drug.

Furthermore, if a first-generation product is derived from tissue and regulated as a drug, then the second-generation recombinant product