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FOOD AND DRUG ADMINISTRATION

WORKSHOP ON

DEVELOPMENT OF REGULATIONS AND GUIDANCE DOCUMENTS FOR MEDICAL DEVICES REGULATED BY THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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P R O C E E D I N G S

DR. DONLON: I want to welcome you all here at the Mazur Auditorium at the NIH, to the open forum on development of regulations and guidance documents for medical devices regulated by the Center for Biologics Evaluation and Research.

I want to point out that we have connected up video conferencing, four sites across the country, and we are welcoming them, a site in Boston, one in Denver, one in Los Angeles, and one in Alameda, California. For those sites that I just mentioned, they can submit questions at any time during the discussions this afternoon. They can submit the questions through faxing. I believe you have the fax number at your site, but I will repeat it here: 301-496-2499. And you can fax questions at any time during the discussion. We will bring them up to the panel and work with them

Again, welcome to the open forum. I am Dr. Donlon from the Center for Biologics. I am one of the co-chairs of the Device Action Plan in the Center. I want to first acknowledge the work of Gail Sherman and her staff in putting this conference together in a short period of time, also specifically Melanie Whalen, who worked directly on the conference and organizing many of these technical arrangements we have today.

As many of you know, about a year ago, through the results of some stakeholders' meetings and some individual forums that we conducted here at CBER, we generated a Device Action Plan relative to devices regulated by CBER. This Device Action Plan was finalized and signed off and published in April of this year. We effectively have about six months' worth of operation for that plan, and we published recently on our web site a six-month report.

This meeting today is one meeting that is addressing a particular point that was raised during many of the discussions from previous stakeholders' meetings internally in our Device Action Plan discussions regarding the need to interact and communicate with industry, specifically in the area of guidance development.

So the purpose of this meeting is twofold. One is to present to you some of the policy and procedural activities that go into guidance development in the centers and the agencies. And on your part we are listening, we are in a listening mode to hear what specific areas you would prefer or would suggest as priorities for guidance development in the area of device regulation in CBER. So we are interested in hearing where we should direct some of our guidance activities.

We started a little late here so I want to get directly to the agenda. First on the agenda we have Dr.

Kathryn Zoon, who is the Director of the Center for Biologics Evaluation and Research, and she will give us some opening remarks. Dr. Zoon?

DR. ZOON: Thank you very much, Jerry, and welcome to all of you. This is another in a number of opportunities we have made to reach out and talk to our stakeholders in a variety of different venues in order to make sure that the Center is appropriately listening to our stakeholders and understanding the needs of the stakeholders, as well as working with our own staff internally to perform a Public Health Service objective of making sure that the devices that the Center for Biologics regulates are safe and effective.

And we believe that in moving forward with our Device Action Plan, as was stated by Dr. Donlon, that was signed off last April, is a true spirit of reaching out and trying to understand the needs of the communities we serve--the industry, the public, the academic institutions, the small businesses--and really try to make sure that the efforts that we are putting into performing our work really have the maximum public health benefit.

So to do that, as you know, we have developed the Device Action Plan, and after having heard a variety of different comments from the stakeholders, our team went back and drafted a series of initiatives that dealt with

performance goals, training of CBER staff, communication internally and externally, and increased coordination and harmonization with our colleagues from the Center for Devices. These initiatives very much were based on the feedback that we have heard from you.

And, as Dr. Donlon said, today is a day that we are actually focusing on one area. Many times we have been asked and it has been asked and it has been asked to the Center, how can we help you? How can we interact with you and give you drafts or position papers that you can use to consider and weigh in on your decisionmaking as it relates to biological devices?

And this is very important, and we want to make sure that today we can provide some information back to you on good guidance practices and how they relate to the documents with the medical devices that CBER regulates, and also hear some of your ideas that might come back and help us do our jobs better.

We have had a great deal of progress on our Device Action Plan. I commend the staff at CBER, and our interactions and contributions from our colleagues in both the Center for Devices and the Office of Regulatory Affairs, as well as other organizational units in FDA, and the input we have received from the outside. So today I believe we will continue the dialogue with you and hopefully continue

in our successful path on implementing the Device Action Plan.

I might mention that one new activity we have added to CBER's repertoire has been a Vendors Day. This is not new to many of you who are in devices, who have worked with CDRH, but it was new for CBER to have such an event, and this was very, very successful this year, and we anticipate holding future Vendor Days, and would ask all of you to continue to work with us on making that a success, as well.

Well, today is your day. We will be providing some opening talks to frame the rest of the conversations and discussions today. Your hand-outs have valuable information that includes information on the Action Plan and updates on where CBER is with the Action Plan, and we would value the feedback of all of you and your colleagues, both who are here today and those who may not be able to make it today. So thank you very much.

It is now a great pleasure for me to introduce Peggy Dotzel. Peggy is the Acting Associate Commissioner for Policy in the Office of the Commissioner, and Peggy has been instrumental from many aspects of developing the entire Good Guidance Policy with input from various components in the Center. And it has been a great pleasure working with Peggy, and we are delighted she could be here with us today

to give an overview on this important subject. So, Peggy, thank you.

MS. DOTZEL: Thank you, Kathy. Can you hear me? Okay, I am just going to--I would like to give you all a quick overview of the agency's Good Guidance Practices. We will start--the topics that I will cover this afternoon are, What are GGPs? Why did FDA develop them? How does the Modernization Act, the recently enacted Modernization Act, affect GGPs? And exactly what are involved with GGPs?

We will start with the basic: What are GGPs? The GGPs are FDA's policies and procedures for developing, issuing and using guidance documents. They are what we call the agency's Good Guidance Practices, and they were issued by FDA in February 1997 after going through a comment process. We put out a proposal, we held a public meeting, and then we issued a final GGP document.

Why did we develop GGPs? Well, there were a number of reasons. I think one of the things that was instrumental was a citizens' petition that was filed in 1995 by the Indiana Medical Device Manufacturer's Council. In the citizens' petition, IMDMC criticized how FDA was developing and using guidance documents. The citizens' petition urged the agency to use notice and comment rulemaking to develop guidance documents.

After considering the citizens' petition, we

denied the part of the petition that was requesting that the agency use notice and comment rulemaking, but we took the opportunity to define what we now call the Good Guidance Practices. Even though the agency disagreed that we should use notice and comment rulemaking to issue guidance documents, we did agree that there were some issues related to public participation in the development of guidance documents as well as issues related to how the various components of the agency work to use guidance documents. There were inconsistencies with nomenclature of guidance documents, inconsistencies with the level of sign-off for guidance documents, and so the agency decided that it was an appropriate time to evaluate this and to try to develop some standardized procedures.

In 1997 Congress passed the Modernization Act. There is a provision, Section 405 of the Modernization Act, which basically took a large part of the main points of FDA's GGP document and codified that. The statute also directs FDA to issue regulations implementing its Good Guidance Practices in a manner consistent with the statute, and the deadline for issuing those regulations is July 2000, and the agency is currently working on that.

Now, to get into the specifics of GGPs, we will talk about a number of different things: the definition of guidance documents; the legal effects; how the agency

applies Good Guidance Practices; our procedures for developing guidance documents; what are the standard elements for guidance documents; how we are implementing our GGPs; how we are making guidance documents available to the public; how the agency is monitoring the agency's use of the Good Guidance Practices; and how the agency is providing the public an opportunity to come back and appeal the way the agency or some part of the agency is applying Good Guidance Practices.

The definition of guidance documents: Guidance documents in general I think describe the agency's policy and regulatory approach to an issue. They establish enforcement and inspection policies and procedures. And, more specifically, it can relate to the processing, content and evaluation and approval of submissions, or it can relate to things such as the design, production, manufacturing and testing of regulated products.

What guidance documents do not include are documents that relate to FDA internal procedures; to agency reports that are provided to the public; to general consumer information documents; to speeches, journal articles and editorials, media interviews, press materials, warning letters, and other communications directed to individual persons or firms.

Having said that, one of the things--and I will

talk about this a little bit more later--that we have tried to make clear internally is that even though these particular things are not considered guidance documents, they also shouldn't be used as guidance. We shouldn't use any of the latter listed things to first communicate a new policy to a broad public audience.

Obviously, the agency is asked specific questions by companies about their specific products or specific circumstances that they have, and obviously the agency has to be in a position to answer those questions, but if we are repeatedly asked the same question, I think that can signal the need for guidance, and the agency should then consider issuing a guidance document in that area.

The legal effect of guidance documents: Guidance documents are not binding. They don't bind the public and they don't bind FDA. That means that if a sponsor wants to use an alternate method to comply with the statute and regulations, if that method complies with the statute and regulations, that method is acceptable. Having said that, the agency does put these out as our current thinking, and so we have made it an agency policy that we ensure that our own staff doesn't deviate from guidance documents without appropriate justification and supervisory concurrence.

As I said a few minutes ago, FDA staff is expected to adhere to GGPs, and again, initial communications of new

or different regulatory expectations should follow GGPs. They shouldn't--one of the things that the agency had been criticized in the past was making "podium policy." To the extent that the agency wants to announce a new policy in a speech or, you know, at a public meeting, we are striving to get that policy out in a guidance first.

And while the agency may still announce new guidance documents at public meetings, the idea would be that we would have a written policy in place. And, again, as I said before, the policy is that it is okay to answer specific questions about how a policy applies to a specific situation, but again this may signal the need for a guidance document.

Probably the meat of what the agency did in developing its Good Guidance Practices was to develop procedures for soliciting public input for guidance documents. To do this, we have defined two levels of guidance documents.

Level 1 guidance documents are documents that set forth first interpretations of statutory or regulatory requirements, changes in interpretation or policy that are of more than a minor nature, and complex scientific or highly controversial issues. Level 2 documents are basically all other documents. These could be things that set forth a minor change in policy, or it could be that the

agency is just taking an existing policy and putting it into writing, something that, you know, a policy that the agency has been following for a number of years.

The procedures differ for the two levels of documents. For Level 1 documents, public input is required prior to implementation unless there are public health reasons for immediate implementation; there is a new statutory requirement, Executive Order, or court order that requires immediate implementation; or the guidance is presenting a less burdensome policy that is consistent with public health. The reason for this last exception is, we wouldn't want to continue to have a policy that was more burdensome if the plan was to start to alleviate some of the burden, as long as that was consistent with public health.

For Level 1 guidance documents, what the agency typically does is we issue a Notice of Availability in the Federal Register, announcing the availability of a draft of a Level 1 guidance document. At the same time we make that document available on the internet, as well as we make it available in hard copy. In the FR notice we typically list a phone number or a fax number where someone can obtain a hard copy if they can't or do not want to get it off of the internet.

In addition, the agency can hold meetings or workshops, or at times will take a direct guidance document

to an advisory committee. The idea is that we will try to get public input at the earliest stages of development.

I think that there have been some concerns that the agency waits to get public input after it issues a draft guidance document, and I think the concern is that maybe the agency's thinking is, it is set in stone and we won't really listen to comments. And I think part of the reason we use the comment process, as in rulemaking, because we are interested in receiving comments.

But the agency has at times, and when it is appropriate we will put out even earlier drafts of documents, even when they are in the concept stage, the idea being as long as we make this concept available to the public at large, so that the public at large can communicate its comments, we have taken the appropriate steps.

For Level 2 guidance documents, we typically will solicit public input when we put the document out. And these documents are posted on the World Wide Web, and then the agency periodically issues an FR notice that lists all of the new guidance documents that have been issued in the last time period, so that someone who hasn't become aware of the guidance document on the web can find out through these FR notices.

For all guidance documents, the agency will accept public comments at any time, even after the close of a

comment period on a draft guidance document. And if the agency receives comments that convince the agency that changes to the document are appropriate, then the agency will proceed to make those changes.

A point that I haven't made is that unlike rulemaking, comments that the agency receives on a guidance document, we don't address each and every comment. When you see the document go from draft to final, there is no requirement that the agency explain, as it does in rulemaking, why it has or has not accepted a comment. But the agency is committed to reviewing all of its comments, and typically when you see an FR notice announcing the availability of a final guidance document, the agency often addresses some of the major themes of the comments that it has received.

Other ways that the agency is soliciting public input is, the agency has been putting out in the FR a guidance document agenda. This will tell you what the agency is thinking, in terms of what its thoughts are, where it is going to go next on issuing new guidance documents or revising guidance documents, and we invite the public's comments on that agenda and on additional ideas for revising or issuing new guidance documents.

In addition, the public is invited to submit draft guidance documents to the agency. In that case the agency,

if the agency decides that it is appropriate to issue a guidance document in that area, we will go through the appropriate GGP procedures, put that document out as a draft, and solicit public comment on that before going to final.

The agency has also instituted internal procedures to ensure that there is appropriate clearance of guidance documents. The procedures that are generally being followed for Level 1 guidance documents is that the office director is--the level, at the minimum it is the sign-off of an office director.

In addition, the Office of Policy in the Commissioner's Office will sign off on documents that have significant new policies, and the Office of Chief Counsel will sign off on documents that raise legal questions. I think to date anyway most of the centers actually have sign-off of their Level 1 guidance documents at even a higher level, and Level 2 guidance documents, the minimum requirement is for sign-off at a Division Director or the equivalent in the Office of Regulatory Affairs.

One of the other things we did in GGPs, and this was one of the other criticisms, is we standardized what we called guidance documents. You may recall, and there probably are still documents out there because not all the documents have been revised, different centers were using

different names for guidance documents, and even within the centers there were different names. You had Blue Book Memos, you had--what was your?--Points to Consider. There were sometimes, you know, things were called letters. There were guidelines, there were varying numbers, there were varying names for guidance documents.

And now what we are trying to do is have everything called a guidance document, so that when you see a document you can recognize it as a guidance document. You know the legal significance of the document and you know the procedures that were used.

That is not to say, like I said, that there aren't some documents still out there under the old names, but we are, as we go through the process for revising documents, we will change the names and try to make this consistent. But because of the number of documents that are out there, we couldn't commit to changing all of the names of all of the documents within a specified period of time.

The documents as they are being issued now also include a statement of the nonbinding effect, so that it is clear to everyone that these documents are not binding. And, in addition, we have taken steps to make sure that the documents don't include mandatory language. They don't say things like "must" and "require" and "shall." Now, the language may be in there to the extent that it is describing

a statutory or regulatory requirement, but we try to make clear that that is what it is describing, is a statutory or regulatory requirement, as opposed to a policy that is set out in the guidance document itself.

And as far as making these documents available to the public, the agency has been keeping a list of guidance documents on the internet. It is arranged by center, and typically you start out at a centralized place and then go to the specific center listings, and in addition the agency is issuing an annual list of its guidance documents with updates to that list, so that people can--people who are not using the internet can keep apprised of what developments are in the guidance document area.

The agency has also committed to monitoring the development and use of guidance documents to ensure that we are in fact complying with our Good Guidance Practices. I know that I get calls and questions about this all the time, and I know that people in the centers get the same thing.

And as with any new procedure, I think over the course of time--in the very beginning there were a lot of questions and probably even some inconsistencies. But I think people have really--the centers have all done training for the people in their centers who develop and issue guidance documents and use guidance documents, and I think that--I know for me the number of questions has really gone

down. But we do--but we continue to monitor that, and as part of developing regulations to comply with the Modernization Act, we have also undertaken to look at how well the GGPs have been working.

And then, finally, the Good Guidance Practices set forth procedures for appeals. To the extent that there is a problem with the way the agency is using or developing or issuing those guidance documents, the document sets forth the way that you can come to the agency to lodge a complaint. Typically it should go up the chain of command, but if that is not working, the document also directs you to the Ombudsman's Office.

And I think that is about it for an overview. I unfortunately have to leave, but I am happy to take some questions before I do.

DR. DONLON: Are there any questions? Are there any questions?

[No response.]

DR. DONLON: Thank you very much, Peggy, for a very concise and brief presentation.

Moving forward, our next presenter will be Richard Lewis. Dr. Lewis is the Deputy Director in the Office of Blood Research and Review. The Center for Biologics, about 95 percent of the devices that we regulate are in this office, so we decided to feature Richard and the Office of

Blood Research and Review. He is going to speak about device and guidance development in the Office of Blood Research and Review.

DR. LEWIS: Thank you, Dr. Donlon. I just wanted to make a few comments about the scope of the Blood Program, the history of how we have issued guidance in the past, and to mention some of the topics that we think are important and are some of our priorities in developing guidance now. Predominantly, though, we are all in the listening mode and want to hear your opinions in terms of prioritization.

The Blood Program, as you know, is very broad in scope, in that we have regulatory authority over blood centers and plasma, source plasma centers. We have regulatory authority over plasma derivatives. We oversee devices that manufacture blood and blood products, as well as devices that are used for testing of blood and blood products.

Some of the regulatory mechanisms that are used, we use virtually all regulatory mechanisms of the FDA. We presently have PLAs, ELAs and supplements, which soon will have seen their day as we move into BLAs and BLA supplements. There still will be a lot release as a mechanism for overseeing some of these products; in particular, a mechanism for looking at the quality as well as the potency of biological products related to blood. We

also have in our office PMAs and their supplements, 510(k)s, abbreviated 510(k)s, special 510(k)s. Not listed here are NDAs and ANDAs.

The Office of Blood we hope has an integrated program of regulatory oversight, in that we are responsible for the national blood policy and the nation's blood supply. It is a responsibility that we take very seriously, recognizing that it is a program of high public concern.

Some of our objectives are, of course, by mandate that products are safe and effective, and as well we hope to see that we regulate in a consistent manner. Some of our testing devices are unique in their standards for blood screening, in that we have an opportunity only once to test a particular blood product, where some diagnostic tests are seen in the context of an overall clinical picture. Again, with testing of blood products it is either a go or a no-go decision, based on the results of a particular test.

Some numbers, briefly. These are estimates that I put together to demonstrate that devices are an integral part of how we develop guidances in the Office of Blood. Of the last 65 guidance documents from the Office of Blood, 25 of those deal specifically with devices or are related to the devices, either in how the device is used, if it is a policy, or our policy on how the results of the testing are applied in blood centers; how reviewers should evaluate some

of these devices in terms of whether or not they meet our particular standards; and well as some of the guidance documents describe standards.

Looking at it in the opposite direction, of 56 devices that we have recently cleared or approved, 15 of those have guidance documents that are either related or associated. So 40 percent of our guidance documents deal with devices, and about 25 percent of our devices have guidance documents that are related to them. Again, this is we hope an integrated program of regulatory oversight of blood.

You heard just a couple of minutes ago from Ms. Dotzel about how guidance documents had varied forms in the past, and we have had Memorandum to Registered Blood Establishments, we have used a Memorandum to Registered Blood and Source Plasma Establishments, a Memorandum to Licensed Establishments. We have used guidelines and Points to Consider.

And, as of February of '97, we are using Good Guidance Practices. We are issuing now guidance for industry, reviewer guidance, and compliance guidance.

The need for guidance is developed in a number of ways. In how we decide whether or not a particular guidance is necessary based on industry input, even though today is a start I think in terms of public meeting to hear your

comments, there are other ways and we have heard other ways in the past that industry tells us what they think is necessary.

We have close congressional oversight on how we operate, and from them we hear what are priorities in the national blood program. Quite often our guidance is developed because of particular products, because of new technologies and the advancement of new scientific methods, as well as our concerns for the public health and our recognized need to address particular issues.

The next couple of slides list what we see are our guidances that we are moving toward their development. They are prioritized in current major priorities and additional priorities because we are--I put them into two groups because we can't actually say this is our top and this is our second and this is our third, because we are working on a number of these things all at the same time, and necessarily, because of the way guidances are developed, it is not necessary to take one right after the other.

We are presently, because of the technology of NAT testing, we have a number of guidance documents in development that address the strategy for testing pooled plasma, which applies to plasma derivatives; NAT testing as it applies to manufacture and clinical evaluation of in vitro tests for HIV 1 and 2; and HIV antiviral drug

resistance testing. This was a recent topic at our Blood Products Advisory Committee meeting.

Other major guidance priorities include revision of reviewer guidance for blood bank software; guidance for blending, reworking and reprocessing of immunohematologic reagents; and another guidance on product stability related to blood grouping, antiglobulin, and red cell reagents.

Finally, leukoreduction filters, our guidance here, there is a number of areas to be addressed regarding leukoreduction. Our initial concentration is on the actual product itself, how a product is developed, how additional products will be reviewed, what are the particular standards by which we will evaluate these products.

And we also recognize that there is an implementation question on leukoreduction filters, and that will be addressed in a separate initiative, not in the same initiative for the actual product, and those are also under development. Additionally, guidances for cell separation devices, specifically addressing the product; as well as blood collection and processing kits.

Finally, additional guidance that we are developing, the external controls refers to our effort to coincide with recent decisions on clear policy on how particular controls are applied to test kits; reviewer guidance for the submissions on hepatitis donor screening as

well as confirmatory assays; reviewer guidance for HIV diagnostic testing, to include rapid tests. We hope to update the 1989, what was Points to Consider for HIV testing for blood screening; and hope to update and develop reentry algorithms for HIV, HCV, HTLV, and anti-Hepatitis B core.

And, finally, additional guidance is presently being developed for anticoagulant and additive solutions for blood collection and storage. This first bullet, someone asked me did this indicate a change in policy, in that it is listed under devices. No, these we still see as NDAs and ANDAs. Then, also, adhesives and solvents in blood containers.

So hopefully you have an idea, both on these slides and in your handouts, what we think are the major priorities for the development of guidances as well as the things that are on our radar screen as things that we hopefully will be addressing in the future. We will be happy to hear your comments today on what you think are priorities and how you would categorize some of these things, and any additional guidances that you think are necessary for development. Thank you.

DR. DONLON: Thank you, Richard.

We will be taking questions at the end of the-- after the next two presentations, and I would remind our off-site participants that they can at any time fax in their

questions to 301-496-2499.

The next presentation will be given by Steve Falter, who is our Director of the Regulations and Policy Staff. Steve will present the CBER priorities in the development of regulations and guidance documents. Ready, Steve?

MR. FALTER: Since I don't plan to make any shadow figures on the screen, I think I'll move over here to where I can see.

As Jerry said, I head the group that deals with regulations and policy development, and primarily that means rulemaking. We do get involved in the guidance document process. However, that is usually late in the game, mainly as a surrogate of Peg Dotzel's to make sure it meets all the agency requirements.

And today, briefly, I just wanted to go over, one, how CBER develops its various regulatory policies, and then I wanted to outline what are a few of the more significant actions that I expect to be happening within the next year or so. Not all of them may be--maybe not all of them will be of direct interest to devices, but I think it is important you realize the overall scope of what we are involved with.

Now, there should be a chart there. Yes. First, what we are up against. Recognizing that, among others, the

device industry has some concerns, it may ask for changes in policies, whatever, you are not alone. And seemingly after so many years I guess there is limited ability agency-wide as to how many changes we can form. As you can see, while we can pretty much meet the needs as far as guidance documents, issuing approximately 20 each year, and some of those take too long, but at least eventually almost all of them get done and out there and finished.

The actual rulemaking is a considerably more burdensome process. You may not be able to read the charts too well, but it lists proposed rules and final rules. The final rules also include some direct final rules. We set a record last year of eight. We currently have 29 pending rulemakings. So when determining priorities, it is a considerable task.

Now, there are many outside forces that may result in prioritization: Congress; public health needs; the industry may request a change; a change in the law; whatever. But to keep us from all being babbling idiots, the prioritization is actually done by the Associate Director for Policy, now acting, Bob Yeter. I can't remember the person before. And we act upon that in tasking the various CBER forces, in getting accomplishments done.

And as you will see in minute, there are a number of outside forces working on us that are setting our agenda.

It is very much unlike the, shall I say, "good old days" when many of the projects that were undertaken came from within the agency rather than from the forces outside of us.

Something else that has changed is, generally we work through a task group. This is something new to us, something maybe in the last several years. This means that for the industry there may be multiple points of input or to ask questions or something like that.

It also represents a considerable more commitment of Center energies to development of policies, both guidance and rulemaking, in that rather than one expert on the area and one person on my staff putting a document together, usually it is a commitment by a number of people to work intensively to get these projects done, mainly because of the scope of what we have had to undertake recently, and I will be getting into that more quite quickly.

Now, while they are putting the document together, nearly everyone wants to get involved, too many in my opinion, and that includes the department and the Office of OMB. They are the ones that make the cut. They look at a short briefing document, determine if they are going to get actually hands-on involved in the review of our projects.

So really I can't tell you until they have told us whether the department or OMB is going to review it. I am often asked to guess, and because I am a baseball fan, I

have a very good record, somewhere around 50 percent, in guessing right on whether they are going to look at documents or not. But this is something that further extends the length of time for the preparation of our documents.

Now, something in the rulemaking process that I have always considered could be a valuable tool and isn't, is that we are required for anything involving paperwork, defined in the very broad sense of either requiring some sort of communication to us or someone else or keeping records on yourself, we have to evaluate the paperwork impact.

Now too often, both within the agency and by the regulated industry, there is arguments over how big the numbers should be. And that never--and while we will always look at the arguments and change the numbers as needed, it rarely results in any change in policy.

What should be the point and what can be the point, if the focus is simply directed toward it, regardless of what the figure that we have calculated and published in the document as far as the paperwork burdens, if it can be lessened and still achieve the same purpose, certainly that would be a wonderful argument to offer and something that we would be very glad to see. Most often we get numbers that, "No, you shouldn't have 50, it should be 80," and really

that doesn't change the policy any, and usually it just represents a miscommunication on what we are trying to calculate.

Okay, on the next, I should also mention that there is also, after you consider the legal and enforcement implications, even though most of our rulemaking is scientifically oriented, they have to be in accordance with the law, they have to be enforceable by our compliance folk.

Very often flexibility and clarity are in direct conflict with each other. Each has their own positive attributes, but that often results in very precise rulemaking simply because it is easy to understand, easy to enforce, where it may not provide the flexibility in the regulations that might be desired by the industry and indeed by us.

Now the primary part in rulemaking where the industry comes in, is in the comment process. We issue a proposed rule, ask for public comments. Something that is lacking much too much, and I don't have the solution for it, is the earlier input by industry, primarily because it is both an ethical and a legal concern that in the development of policy, everyone have their say.

So to listen to one organization, even though it is a very broad-based organization, is very difficult when developing policies. Under the Administrative Procedures

Act, we have to have an open forum. We can't assume that one organization, one trade association, represents everyone's thinking.

In a way, that is a shame. I think our work would be much easier. I hope that mechanisms do come about where we are able to directly relate to associations more. I will have one example in a moment where we have done just that, but that is still a problem.

So, anyway, we depend on these comments. They are looked at very carefully. Almost 100 percent of the time, changes are made in our rulemaking documents at the final rule stage as a result of public comment.

And I just wanted to quickly provide a few pieces of advice so that your voice may be heard perhaps a little bit better. One of the biggest problems is that often we get comments from the public which are critical of what we are doing. We are used to that; it doesn't bother us. But often they are just a general complaint and we don't know what they would like as an alternative.

It is very easy as human beings just to ignore something if it just seems to be a gripe. If they give a specific set of how they think things should be, it is something that everyone has to carefully consider. It is amazing how often, when we look at a letter comment, where there are paragraphs complaining about a provision and you

end up having no idea what they are talking about. None of you out there would do that, I am sure.

And the other thing that I try to emphasize that is often overlooked is that many of our rulings may be controversial within the industry itself. Some may agree with it, some may disagree, and if you agree, you should say so. It is much easier to reach resolution if there are parties that agree with what we are trying to do as well as those opposed. If we get three people opposing and nobody seems to agree, then it seems to balance the scales somewhere out in the other direction. So, please, if by some rare chance you actually support what regulation change we are doing, please say so, and that will help us when briefing the management as to reaching a final decision on the action.

One thing that is often omitted in public comments and that I have to force considerable thought about within FDA, a set of regulations or reg changes may be fine, but people don't think about just how are they going to be implemented. What is the timing going to be? How long are they going to have? How much advance notice? Can they do this?

And so we try in our proposed rules, it is not in the codified section, but in the preamble we try to describe our proposed method for implementing a given set of changes,

and I think careful focus should be put on that because often after the fact, after we are done issuing a final rule, that is when we get the complaints: Gee, I can't get this done in time? What can I do? And while we do try to accommodate people, it would be much easier if these problems were anticipated beforehand.

Okay, the next slide. Now I am getting into very specifics. Many of our priorities aren't single projects but overall programs that are being addressed, and so we have this thing called Action Plans. There's three of them there.

It's curious, I haven't listed the Device Action Plan, but primarily that is not a rulemaking process. There is one case where we may revise some reagent standards. But if you read the device action plan, it largely deals with the internal workings and mechanisms of the agency. We rely on device regs, same as Center for Devices do, unless it is a licensed product, in which case we deal with the licensing regulations, so I haven't included that in the list.

The first three, the Blood Action Plan, Tissue Action Plan, Xeno Action Plan, I am going to go through very quickly. FDAMA, I won't have anything more to say on. A lot of that has been done. There has been a lot of publicity, a lot of it is multiple centers within the agency, and it is just too much to deal with in this short

period of time.

So on the next slide, first of all, the biggie is the Blood Action Plan, pretty much a comprehensive look at our regulation of blood, plasma, blood derivatives. A lot of it is ongoing. I have created some small print here, not just to torture you, but more for the carry-away value. Where we have already taken an action in this area, I have provided you a Federal Register reference if you have further interest in the subject.

And, once again, not all of these are directly device-related, although many of them deal with testing issues which involve test kits, so your interest may vary as far as each individual project. Much of it deals with blood banking per se. The first, the Hepatitis C lookback, both presented in a guidance and a proposed rule. "Error and Accident" reporting for blood banks, we have already issued a proposed rule to a final rule.

And something I should mention, because that brings to mind one of the more profound changes you will see in our regulations upcoming as we deal at least with brand-new regulations, is we are starting to write in what is formally called "plain language." This does not only mean simple language. It is a given format for understanding the regulations.

I think it is a vast improvement, and you will be

seeing some examples within the next year from our Center. Other centers have already issued some things. But basically what we are doing is, we are replacing--we are sacrificing what might be the most succinct way to present regulations, to have greater clarity in the regulations, in the way it is presented. It is something that I support, and I think above and beyond simply looking at the substance to the rules, if you prefer that as a regulation form, we would be glad to hear from you.

And, once again going back to the list, we have already issued a proposed rule that totally updates and revises, for blood and plasma donors, what the testing requirements are. Notification of deferred donors is another thing to do with blood donors. I won't get into that because it is not device-related.

And basically what we are doing is totally revamping how we deal with blood science. You know, I can answer questions about some of these specifics later on, but if you should have any questions, but I don't plan to get into the individual projects. Most of them have either already published in some form or there already has been some public pronouncement of our intent to undertake these projects.

On the next slide, however, there is something that is of considerable interest to all. We are testing out

a pilot program for dealing with blood licenses where there are redundant changes in the area of blood banking such as the irradiation of red blood cells, and this could be things involving the device industry.

Rather than having each submitting all the information to demonstrate that they are going to make the change satisfactorily, the agency is testing out the idea of us preparing a document as to what we think is satisfactory, at least one way of doing it. And if each blood establishment agrees, they can certify that that is what they intend to do, thereby tremendously abbreviating how much information they have to submit in to the agency, with the idea that as long as they are committed to doing it this way, we can evaluate through inspection whether indeed they are doing it that way, and in this manner a lot less paperwork will be going back and forth.

This is something to consider if there is a new medical device that would be used in the blood banking industry, in that as an ease for your clients in getting it adapted into their program, if this program works, it could really change the way we deal with the numerous blood banks that we license.

And something, another thing I didn't describe too well but it is a rare bird indeed, is we have--well, it wasn't "we"--the industry revised the labeling for blood and

blood components to accommodate new bar coding and otherwise do a few updates as to how business is being done, and we have adopted this as to be--and we are completing the process--to be our own guidance as to how we recommend that blood be labeled.

This was something that was quite difficult to get through, much to my consternation, simply because it wasn't an FDA project. It was something that was said and done by industry and then given to us, and there really--GGPs, while it speaks to the issue, really does not have a process that accommodates the development of guidance by industry with the eventual adoption by FDA.

I think it is something that both the industry and FDA has to work on so that we can work more closely together, considering that often much of the expertise is within the industry as far as areas of interest where we might want to develop guidance. The regulations are actually fairly minor changes to accommodate the new bar code technology that will be adopted.

Okay, and the next slide. And I present this by and large more to present the scope of what the Center is working on. For those of you who don't know, xenotransplantation simply deals with animal organs or other tissues in treatment of humans. It is not the formal definition but it will do for now.

That has involved a tremendous amount of effort on our part, since it is a very cutting edge and controversial area of science, and has involved a lot of consideration both by us and the department, resulting in both a Public Health Service guidance, and FDA guidance that we expect to issue next year, and also the beginnings of some regulations that deal not only with xenotransplantation but gene therapy, in which we are going to prescribe standards on how we are going to interrelate with the public in general in providing information related to the clinical study of these various forms of therapies. So that is also an area of great interest and time consumption to us.

Something of slightly more interest is on the next slide. Finally, the last action plan. If there is another one, I am quitting. But we have already--we are expanding our interest in the area of tissue. We have regulated tissue banking for quite some time, but we are expanding both the regulations and proposing to expand the area that we regulate to include the standard registration mode that you are all familiar with dealing with tissue donors and, finally, good tissue practice. All these may involve in some way the device use, such as donor testing, and in good tissue practice, which is kind of a new term as a substitute for GMP.

So I have only given you a sampling of what we are

involved in. There is far more to be done, but right now most of our efforts are involved in these various action plans. There are some specific device projects that are ongoing, none of them of the great scope of these projects, but I might in a limited sort of way be able to answer questions on those later. Thank you very much.

DR. DONLON: Thank you, Steve. I just want to point out for the record, remind you that Peggy Dotzel in her presentation indicated that guidance development is not rulemaking. Steve presented some discussions of some of the rulemaking process that his staff primarily goes through, more as an illustration of the process, which includes also the ability to get comments into whether it is a rulemaking or a guidance document. I don't think he is implying that we are going under guidance development as rulemaking.

Our next and final presentation before the question and answer session is from our--essentially Steve Falter's counterpart at the Center for Devices and Radiological Health, Joe Sheehan. Joe Sheehan is the Chief of the Regulations Staff in the Center for Devices and Radiological Health, and will also discuss CDRH priorities in development of regulations and guidance documents. Joe?

MR. SHEEHAN: Thank you. Good afternoon. I would like to tell you a little bit about how the Center for Devices establishes its priorities for developing

regulations and guidance, and tell you a little bit about our criteria for establishing priorities and our procedures, in the hope that you will understand them better and be able to participate yourself in the guidance and regulations development process.

The primary criteria we use are, of course, the public health is job one, and everything in one way or another has to be related to the public health. And the other criteria, again, are all interrelated with the public health, and these criteria, as we will see further one, one or more of these criteria can apply to any particular regulation and to how it is prioritized by the Center.

There are statutory mandates of one kind or another which obviously are very important. There is workload considerations of various kinds that unfortunately we have to take into consideration. We don't always have time to do all the things that we would like to do, so we have to take into consideration our work load. And also there are various types of requests from outside: petitions, correspondence, just people talking to people in the Center and giving them ideas for regulations or guidance.

In the Center we primarily once a month, usually on or about the first Friday of the month, we get together the people from the various offices in the Center who are

primarily involved in regulations, and people from outside the Center, within FDA, who also help us with the development of regulations and guidance, and we talk about all the various issues that are related, and try to come out of that meeting with priorities for what we want to do, particularly in the next month.

We can talk not only about what the status is of the regulations and guidances we are working on at that time, and what it will take to get those done, but also some perhaps new ideas for regulations or guidances to be developed in the future. Somebody may say, "This issue came to light or that issue came to light, we're thinking about developing a regulation or a guidance to do that," and that gets onto the work plan and we begin to figure out how we are going to prioritize that.

And once every three months that is turned into a quarterly meeting. The monthly meetings are chaired generally by the Deputy for Regulations and Policy, Linda Kahan. The quarterly meetings, the Center Director, Dr. Feigal, would come in, and each of the office directors would also be there to give a little greater emphasis to establishing priorities from their point of view.

And then twice a year we publish our semiannual agenda. FDA and the whole government publishes its semiannual agenda, and you can get some idea from that what

the very highest priorities of FDA and of each of the centers are in terms of developing regulations.

And how can you affect that process? Like I said, you can talk to the people that you know in the Center that are involved in a particular program, tell them you think you need a regulation or a guidance. They also should be talking to you. We would hope--we have a new, reengineered regulations development process in the Center which we have been doing for a couple of years and we are continuing to refine, and the first stage is really to do a concept paper, to try to figure out what is the problem, how should we address it, and if we determine it needs a regulation or a guidance, what should be the particular parameters of that regulation or guidance.

And it certainly should be part of the job of the person or persons who are developing that concept paper to take into consideration affected parties outside of FDA and the public and the industry and the health care community and so on, what their point of view is and what their particular input would be to that process, and they should try to get that, to the extent that it is helpful. And, if appropriate, there also should be public meetings or other particular public announcements, so that people have an opportunity to participate even before we get into the actual development of a regulation.

Some examples of regulations we are working on now that have particular public health considerations, where the primary impetus is the regulation, we published earlier this year a proposal on surgeon/patient examination gloves. It reclassifies those devices according to the powder residue left on the gloves. That came to light as a large part because of concerns expressed by the health care community about the effects of powder on gloves to their particular workplace.

Hearing aids is another regulation we are working on that came to light from the various affected parties in the health care community and in the affected patients and so on, that felt that there was a need that we should update the regulation that we have had in effect since 1976.

And of course reuse is an issue that came to our attention from various points of view, primarily health-related. We are listening to various points of view. We are going to have public meetings. There are opportunities to participate in that already, and there will be more before we even get to the stage of a proposal, if that is what it ends up being.

Then there are statutory mandates. A good example of that is FDAMA. In some cases the statutory mandate is specific, such as FDAMA said that we need to have intended use guidance by, I believe, nine months after the FDAMA was

passed, so that obviously becomes a very high priority to get that done in that time.

Another very specific statutory mandate in FDAMA was the provision on IDE supplements, where it said we had to have a rule in effect to implement that provision within one year after the effective date, so obviously that too had a very high priority consideration.

Then there are other statutory mandates where it didn't specifically require us to develop a regulation or a guidance within a specific period of time, but that was the best way we could get our work done. For example, the FDAMA established this new 100-day meeting, where you could meet with FDA within 100 days after they had filed a PMA to discuss the progress of it and what it would take to get it to completion.

Obviously, we needed to set up some procedures for that as fast as possible. That went into effect for all PMAs that were filed as of the effective date of FDAMA, so we had to get some procedures into effect so that everybody knew what we were doing in implementing that, and that it was done in a fair and consistent way.

Similarly, the "least burdensome" guidance, something that certainly needed to be considered, and needed a guidance document to some extent that came from some outside request that we needed a guidance, and people

thought that we should move it up to a higher priority, and so we did.

And another example is the de novo classification, where you get a "not substantially equivalent" letter in response to your 510(k) and you can come in with a request that it be reclassified into something other than Class II or Class--other than Class III, where it would be classified as being not substantially equivalent, you could get it reclassified. Well, that was to go into effect as of February 19th, I guess, three months after enactment.

And we felt that, well, we don't want people just dumping stuff on us, because this had a very tight time frame. So we had to get a procedural guidance out on how to implement that as soon as possible, so that we would be prepared to receive these and receive them in a way that we could process them very quickly and in time with the statutory time frames.

An older type of a statutory mandate that affects us a lot in terms of guidance documents especially is the Preamendments Class III Devices. When we first classified devices into Class III as a result of the 1976 amendments, premarket approval applications were not required until we asked for them through a notice and comment rulemaking process.

Well, there were about 138 devices that fell into

that category, that were reclassified between say 1978, and the last classification was 1988, and I believe as of 1990 when the Safe Medical Devices Act was passed, 110 of those devices, we still had not called for PMAs or reclassified them. So there was a provision in the Safe Medical Devices Act of 1990 that said, "FDA, you've either got to reclassify these devices out of Class III or call for the PMAs, so within five years you've got to have a plan for doing that, either reclassify them or call for the PMAs."

So in 1994 we put out a notice saying--putting these devices in three categories: The ones that we thought were basically disused devices, were not really on the market anymore, and really we just called for PMAs for those and there were basically no responses, so that took them off our list. There were other devices that we thought could likely be reclassified, and we invited reclassification petitions for those.

And a third set of devices that we thought could not likely be reclassified, and we would likely call for PMAs, and we had a very general schedule for them. In that case also manufacturers could still submit reclassification petitions, but we sort of warned them that it was less likely that we were to grant those.

So that resulted in a lot of guidance documents because, one, for the devices for which we were going to

call for PMAs, guidance documents were needed in order to tell manufacturers what they needed to submit in their PMAs. But the most common type of guidance document we have now are the reclassification guidances.

The SMDA also added a provision that allowed Class II devices to be regulated not only by performance standards but by special controls, and it included as a special control a guidance document. So now the most common special control for these devices that are being reclassified is a guidance document, so if you are seeking reclassification of your device into Class II and you think a guidance document is a very good special control for it, you are certainly welcome to submit as part of your reclassification either a draft guidance document or the outline of a guidance document that we can use as a special control.

And reengineering obviously has been another impetus for developing quite a few guidance documents, such as implementing the PDP requirement and so on, and also in the regulations area where we are working on a regulation now to sort of redo our registration and listing process. And we have had some public meetings on that, and there will be more opportunities for public input before we actually propose the rule.

I might say, to go back to workload considerations, it is not only our workload, that we reduce

our workload, but also in terms of thinking about the Preamendments Class III Devices, calling for the PMAs, we have to take into consideration that they fall into certain categories of cardiovascular, ENT, and so on, and that these fall into certain divisions. And we don't want to overburden one division with getting a lot of PMAs or a lot of reclassification petitions at the same time, so we have to, in establishing priorities, we certainly have to take that into consideration.

And, finally, outside requests are certainly an opportunity for you to submit in the information that we can use in terms of setting our priorities for developing guidance documents. Petitions are certainly one way to do it. I know we are working on one guidance document that is being--is going to be issued at the same time as we issue a response to a petition in terms of prescription device labeling.

Correspondence, if you deal a lot with a particular division in terms of PMAs and 510(k)s and you think a guidance document can be useful in that process, you certainly are invited to submit that. Again, that is part of the GGP process, too. When we publish our GGP agendas, you can see what we are working on and have an opportunity to participate in it.

And, in general, just discussions with ODE

reviewers, when you are talking to them, can work their way into them developing a guidance document because they might see that it is worthwhile both for you and for us. Again, reclassifications and 501(k) exemptions, as we propose those, that is certainly an opportunity for considering guidance documents and regulations that reduce burdens on both of us.

Tampon absorbency labeling, the proposal we published earlier this year, came as a result of an outside request. The manufacturers of these types of products saw a need for us to revise our regulation. They asked us to do it, and that ended up on the proposal that we published. And, again, prescription labeling is the one that I just talked about.

And that brings us to the conclusion, and we certainly invite your participation in the process in the ways that I have outlined.

DR. DONLON: Thank you, Joe. I know that the Center for Devices and Radiological Health had a major role in implementing some of the provisions of FDAMA, and your office particularly was under the gun to perform many of those implementations, and I think your staff did an admirable job.

We are going to proceed now to the questions and answers, and I am going to ask Dr. Kimber Richter to join

the panel. Dr. Richter is a Deputy Director for the Office of Device Evaluation in the Center for Devices and Radiological Health, and she is also one of the CDRH representatives on our Device Action Plan Steering Committee.

I will remind the individuals here in the audience that if they have a question, they should step to one of the microphones in either of the aisles, since the proceedings are being recorded and there will be a transcript developed from the proceedings. For those in our off-site locations, you can step to the fax machine and again use 301-496-2499 for faxing in questions to our panel. Okay?

Now, we have already received one fax and we can probably begin with that. If Dr. Lewis will reveal the contents of that fax and then answer the question, that will be fine.

DR. LEWIS: I will read the questions first and then attempt to address them. There are two questions. The first one: "Given that there are a number of high priority CBER, blood-associated guidance documents pending, when can it be expected that these will become final?"

Well, when these will become final again is a question of prioritization, I guess appropriate for today. Of those that I mentioned, I mentioned nucleic acid testing strategies and HIV antiviral drug resistance testing.

In the last one, for the drug resistance testing, we have recently had a Blood Products Advisory Committee discussion on that, and are working some of those concepts and guidance that we got from our Advisory Committee into a draft document, and hopefully moving on that very quickly.

Similarly for nucleic acid testing strategies. This is a particular technology that we anticipate will be implemented or we will probably see license applications before the end of 1999 or possibly early in 2000, so it is in our best interests as well as that of the blood industry to have an idea of how to implement these particular types of testing strategies.

So those are on a very high priority time line. As to when they will in fact become final, that is a specific answer that I can't address. We try to move these as quickly as possible and have the input from various parts of the FDA that we can. On extremely high priority, we try to have input concurrently rather than sequentially on a number of these particular documents, to try to speed up those time lines, but final dates are very difficult to predict.

And associated with that, "What elements of GGP addresses timely issuance and finalization of guidance documents?" I am reading this as a general question that Peggy Dotzel might have addressed. Specifically to Office

of Blood and our guidances and what is timely, again it is a prioritization question.

And how do we get them out timely? We recognize public health concerns first and foremost in our efforts and attempt to also take into consideration when the technologies will be implemented, so that we can address them for industry who is developing a plan as well as for FDA who is going to be reviewing those data, that we have the appropriate data to implement new technologies as quickly as we can.

DR. DONLON: Okay. Thank you. Are there any other comments on those questions?

DR. LEWIS: Steve wants to add something.

MR. FALTER: Well, Peg asked me to represent her as the GGP person. So admittedly there was a trade-off, in that for greater participation of the public in developing of guidance through a draft and then a final process, it does take longer. That is the price that is paid.

However, you will note from my graph that the number of guidance documents issued per year is pretty much representative of those that were developed, whereas in regulations it is more of which ones of the many projects that we have interest in will we use all our energies to get through.

So though the time that it takes for a guidance

document, it may be disagreeable to some, it is something that does get accomplished and usually is not an extensive delay in getting done, unless there are technical, scientific or policy issues that are interfering with it. So if it is a matter of just simply getting the work done, I think our track record has been pretty good and is even improving.

DR. DONLON: Okay. Thank you very much.

We have a question on the right over here.

MR. HEALY: Yes. My name is Chris Healy, and I am Director of Government Affairs with ABRA, but I am here today on behalf of the Coalition for Blood Safety. Members of the Coalition for Blood Safety include American Association of Blood Banks; ABC, America's Blood Centers; and ABRA. I have just a few questions and a few comments, as well, if you would indulge me for just a minute.

The first of my comments and questions goes to industry input, and we share Mr. Falter's frustrations about early industry input and guidance development. However, we think that there are probably a few new technologies out there that will help facilitate earlier industry input.

We know with the advent of the web and putting early guidance and draft documents up on the web, we think there is an opportunity to meet the public notification requirements of the Administrative Procedures Act while at

the same time sort of vetting concept papers that the agency is developing through industry. We do know there is some precedent for this. We know that the CMC guidance under the BLA was drafted first as a concept paper, and there was a lot of good industry input early on there, and by the time it was published, it was a document that we were all very happy with and could live with quite easily.

We also know that that is pretty much standard operating procedure for CDRH, that often there is early input from industry. We know that the 510(k) modifications guidance was vetted through industry early on, and when that came out, again it was a very acceptable document.

So I am wondering if the agency has a perspective, CBER has a perspective on the use of the web in this way and if there are some real opportunities for early input.

Secondly on the industry input issue, is there an opportunity for an industry liaison at some of the Device Action Plan Task Group meetings? The converse is often true. We know there are FDA liaisons to TTV meetings, TTD meetings and committees, and we are wondering if there is an opportunity for industry representation as a liaison to some of the internal FDA meetings, so that we can be apprised of what is going on, and at a minimum maybe getting some of those meetings' minutes published on the web so that, again, industry is involved in the process, if not actively, at

least passively.

The second set--and I will try and be brief here--the second set goes to agency resources. We are wondering what CBER's plans are to address agency resources. We know that there has been some reshuffling and some loss of personnel, of people at the agency, at CBER, with device expertise. We are wondering what plans are to rely on CDRH for review of submissions when CBER resources might not be adequate to do so.

And we are also wondering what plans the agency has to optimize the authorization process. Currently a lot of products are subject to 510(k) review as well as a thorough licensure review, say for example when a pheresis machine is installed at a plasma pheresis center, at a blood collection center, and this kind of duplicative review both for the 510(k) clearance as well as for the licensure seems somewhat redundant, and maybe there are opportunities there to streamline and maximize agency resources.

So that is it. Thank you.

DR. ZOON: I will try to get them in order.

The first, certainly the idea of a concept sheet and getting put early and having public access to that is one mechanism that I think CBER would certainly support. I believe that clearly that is a way to get, early on where some of the more difficult issues may be or where some of

the time may need to be spent in working through certain issues, to make sure we understand the public comment on a particular proposal. So I think that is one of many mechanisms that might be used.

The issue, again, of meetings and task force, that one is more difficult, because if you invite one person into a meeting, you need to give access to everybody. You can't limit access, so then it becomes a public meeting. And certainly meetings like this that we have, advisory committee meetings where concepts and policy are discussed and people are invited to make comment as early as possible, oftentimes if we will have a document that is in draft, we will hold a workshop on it to get comment, so we try very hard to reach out to all those participants and invite comment on these documents.

I think part of the problem with some of the concept that you had raised is, who gets to come to the meeting? And that is where it gets very difficult, so the only way that we could really deal with this fairly is open it up totally. But we do accept input in terms of white papers that people might want to submit to the agency on a given topic, and so that we can take that under consideration in developing those policies.

As far as--your next question dealt with resources. As we look at resources for the Center, this

year under our current appropriations we were given money particularly and some enhanced resources to apply to the Blood Program, and we are making allocations to help meet some of those needs.

Clearly the retention of critical personnel, especially in a variety of technical areas, not only in blood, is critical for the agency to maintain. And clearly the device area is one that we will continue to strive to get excellent personnel in, both from the scientific perspective as well as the legal perspective, to deal with the issues at hand, and that will be a priority for the upcoming year, to meet some of those goals.

The issue of looking at the workload and our interactions with CDRH, I think CDRH isn't waiting for CBER to give them work. I think they have got quite a bit of their own. But in saying that, we work very closely together on common issues of mutual importance, and I am--right now I think those interactions have been very positive and proactive, and where we can, we help each other.

And clearly their participation here today is a sign that we are working very hard together to harmonize our information and our approaches, and to the level that in times when either center has a particular area, I think both centers have really stepped up to the plate to help each other out, and we could probably name specific ones. One

that comes to mind that CDRH had helped us with was some software policy, and we have been very appreciative of that and the help that they have given us in that area, so I believe that is very important.

The last area where you discussed the issue of looking at duplicative regulation, that is a legitimate issue we need to look at when those cases come up, and those of you who have some specific proposals that you would like to put forward, we would be happy to review those.

MR. HEALY: Thank you.

DR. DONLON: By the way, in regard to the resource part of your question, were you implying that CDRH has more discretionary resources available to them than CBER? No? Okay. Thank you very much.

I would also point out, just in general comment, that the docket for this meeting is open for 60 days, so if you can formulate your comments after this meeting, have some way of formulating your comments and presenting them to the docket in a formal way, those will be taken into consideration as well as the transcript of this meeting.

Do we have a question here on the left?

MR. NORTHROP: I am Steve Northrop, Executive Director of the Medical Device Manufacturers Association in Washington. I appreciated Mr. Falter's comments about one group not necessarily being able to represent the views of

all of industry. I know that is not necessarily convenient all the time for the agency, but when you look at the heterogeneity of this industry, I think it is impossible for one group to speak for everyone.

We are already on record as advocating the transfer of management responsibilities from CBER to CDRH with regard to devices. I won't belabor that point, but I will ask what criteria that CBER used to determine who would be providing the industry perspectives today?

DR. DONLON: It was basically an FR notice which basically invited industry to present in a public meeting. The ones that are on the agenda are the ones that came forward and requested time on the public agenda.

MR. NORTHROP: I will be honest with you, we submitted comments for the docket on October 1st, and I just went and looked at that Federal Register notice and I saw no procedures in there for how an outside agency, an association or company, could petition for a spot on the agenda this afternoon. I may have missed it, but I just relooked at it and didn't see it. So if I'm wrong, I'm wrong, and I will accept that, but I didn't see it.

DR. DONLON: Okay.

MR. NORTHROP: Appreciate it.

DR. DONLON: Surely. We have a couple of fax questions, one here directed I guess to CDRH. There are two

questions directed to CDRH:

"How does CDRH prioritize the guidance documents that are needed?" Joe, or Kim, or--

DR. RICHTER: I will go first. I think we use some of the criteria that are similar to those that were described for regulations. I think we look at areas where we are getting a lot of questions or perhaps there is confusion on the part of industry about what might be necessary for submissions. We look at whether there are scientific changes occurring, that we need to update our expectations, and I think we also look at the number of submissions we are getting.

And then in addition we have to have enough of an understanding of the devices to know what to put in a guidance. So if it is a first of a kind, it is unlikely we would be developing a guidance document. After we have worked through some of the policy issues and the scientific issues and we have a better idea of what we think is important, it is easier for us to do a guidance document, so at that point we might be more likely to draft one.

But I think it depends both on workload and apparent need, and on the scientific situation and whether we think a guidance document would be helpful. Joe?

MR. SHEEHAN: Yes, I agree. I think the criteria that I laid out was meant to apply not only to regulations

but also to guidance documents, that we take into considerations the public health concerns, the workload concerns, and the statutory mandates.

Like I said, a lot of the guidance documents we see are special controls. And therefore if we need to reclassify the device for whatever reason, because we have a petition or because we believe it is in the interest of the public health, or we believe it is best for our workload to shift our work from doing PMAs for this device that isn't really needed to doing it--using it for something more important with more public health benefit, then that is something which we put as a higher priority for reclassifying and therefore also for doing the guidance document.

DR. DONLON: The second question to CDRH is, "How does CDRH make industry aware of guidance or regulations that are in the development phase?

MR. SHEEHAN: Mostly right now it has been a case-by-case basis, as I said. It is the--part of the concept phase is to make sure that industry gets involved. Sometimes we have public meetings. We have had Advance Notices of Proposed Rulemaking, and sometimes we just talk about them at public meetings.

MR. FALTER: If I could interject, agency-wide, is it once a year, we issue a Federal Register notice which

announces all those guidance documents that are currently under development by each of the centers, inviting both comments on those documents and an invitation to state what other areas should be covered through guidance.

I think it is a tool that is fairly new and it is underused so far. It would be very helpful to hear from the public. Isn't one of them about to issue, do you know? I think very shortly the next issue will publish?

DR. DONLON: Okay. I have too a fax that gives a recommendation for guidance documents. It is not in the form of a question, but we can basically comment on this, and this is somewhat directed to the Office of Blood.

The recommendations are: "Develop guidance on leukoreduction of all blood components, platelets, red blood cells, and plasma, assuring harmonization with European and other country requirements."

And the second recommendation: "Develop guidance for pathogen inactivation of blood components, and assure harmonization with other country requirements."

I think one of the factors in both of these is the concern for harmonization, I guess, with European or other country requirements. Can someone address how we take those into consideration? Steve, or Richard?

MR. FALTER: You go first.

DR. LEWIS: Okay. I will let you address the

international harmonization part of it. Is that the hard part?

MR. FALTER: There is no easy part.

DR. LEWIS: In terms of guidance for leukoreduction, as I commented earlier, there is a lot of different factors that we feel like guidance would be necessary for a lot of different aspects, not only on the leukoreduction filters themselves, how they are evaluated as products, but also on the implementation and the degree of implementation of these particular products. And we recognize that there are requirements in other countries that aren't--that don't necessarily coincide with ours, but we have to make our decisions based on our perception of the public health and when it is necessary to take action as well as to implement a risk-benefit analysis.

MR. FALTER: As I just mentioned, the best mechanism is when we ask for input on what guidance should be developed, we would welcome the submission of the one comment. Often, if that comment is well-formed, because it is available to the public it will stimulate more comments, and once you get several people asking for the same thing, it generally will happen.

As far as international coordination, that is a problem. We do have a small group of people that deal with that issue, and we try to keep them informed on what we are

up to, more to avoid disharmony than anything else. And it is something we always welcome advice and information on, because the world is moving so fast, it is very hard to keep up with it.

DR. DONLON: Okay. I have one final fax question here, and I guess--I am not sure if there is an answer to this question, but I will direct it to Richard Lewis: "How soon will serological tests for cadaveric blood be licensed?"

DR. LEWIS: I would refer that to some of the people in our Tissue Group, and in fact that is a question that they are addressing and looking at.

DR. DONLON: I don't think there is an answer to that, because we can't basically say it is going to be licensed on December 31st or something of that nature, but I think Rich is right. People in our review groups are working on that question.

I don't have any more questions, fax questions, and I don't see any additional questions in the audience here, and we are right on schedule for taking a 15-minute break. I will remind people of two things. One, the handouts for Nancy Hornbaker and Carolyn Jones are on the front table or the table in the lobby. We will take a 15-minute break. At that time we will come back and convene the industry presentations, and there will be questions and

answers after those, as well. Thank you.

[Recess.]

DR. DONLON: If the people in back could come in and take a seat, and those speakers who are on the agenda for this afternoon, if they can come forward and get organized, we will get started in about three minutes. So take a seat or leave the auditorium, and we will get started. And welcome back to our off-site locations.

We are beginning now with the industry presentations. In the invitation to the public meeting, we had three requests for presentations, and we will proceed with those presentations and then have, again, questions and answers.

Our first presenter for this afternoon--are you ready, Anna?--is getting prepared with her video equipment. We are making some final adjustments on our computer presentation here. The first presenter from the industry section will be Anna Longwell, who is the Corporate Director for Regulatory Affairs at Becton Dickinson. Anna?

MS. LONGWELL: Hello. Thank you for having me here today and allowing me to speak. I am speaking for my corporation, simply not as a representative of any device organization. However, the company does make devices that are reviewed by CBER and has many more actually in development than we even have in review, so that's the

source of our corporate interest in CBER.

Of course, we want to start FDAMA. I just want to remind everyone that we don't believe that there is an explicit exception for devices that are reviewed by biologics under the 1991 Memorandum of Understanding in the food and drug law. That is, there is no explicit exception for any of the requirements of FDAMA that pertain to devices.

It is our feeling that CBER, in their last publication in the Federal Register in which they actually adopted some of the CDRH guidances, felt that the applicability of those provisions was somewhat unclear, and that they needed to formally adopt these provisions in order to clarify the fact that these requirements under FDAMA also pertain to devices that were reviewed by CBER. We disagree that they were ever unclear, but we're very delighted that CBER acknowledged that those provisions do apply both to devices reviewed by biologics and to devices reviewed by CBER and those reviewed by CDRH.

So, anyway, as we know--okay, as we know, FDAMA provided a number of requirements for devices, among them the development of guidances, and there are a number of CDRH guidances that have been publicly accepted by CBER, many of those that are explicitly required by FDAMA relating to early collaboration meetings, IDE procedures, PMA

procedures. But we have some questions actually about the implementation and the application of those guidances, which is what I am mainly going to address in my presentation, the guidances that have already been accepted by CBER.

Do CBER and CDRH interpret these guidances the same way? At times it appears to us this may not be the case. We would like to see a mechanism by which a common interpretation of a guidance document could be accomplished.

Does CBER have a plan for adopting other CDRH guidances, or was this a one-time thing? We would like, again, a list of guidances, and by this we mean joint guidances under discussion. Software, which has been one that has been the subject of much interaction between CDRH and CBER, is an obvious start.

Again, a question that has come up with some of our regulatory staff: Is CBER really using those guidances, the ones they published their acceptance of? Is there some mechanism to track use of the guidances?

We have heard today about training. We are wondering, is there training of CBER reviewers in the use of CDRH guidances?

Once again, we frankly don't think that a guidance should be accepted by CBER unless CBER reviewers are given the chance to input into it. Were they given a chance to input? It seems difficult for reviewers to have a guidance

that they haven't had a part in developing.

Have they attempted to revise CDRH guidances? Is there any interaction going on in which, say, a guidance would be re-looked at and CBER staff allowed to input into CDRH guidances, if they feel that they're not completely appropriate?

The last one on this list is one that I routinely ask our regulatory staff when they get involved in something new: Have you read the guidances? Do you understand them? And then I start asking specific questions. Does somebody do that for the CBER staff when they proceed to apply a new guidance?

And, again, are you going to issue some joint device guidance documents? Remember, these are products that are, although they are reviewed by two different parts of FDA, are in fact products that are legally devices.

Here are some suggestions that have come from various people at Becton, things they would like to see in the guidances now. We would like to see CBER point persons for each accepted guidance in the guidance documents. We would like to see those guidance documents that were written by CDRH and accepted by CBER republished with comments from CBER staff, and then have public comments on the CBER input.

Once again, we do feel that people shouldn't have guidances shoved down their throats, that everybody should

have a chance to comment. And that means that if CBER is developing a guidance and CBER is subsequently using it, then CBER should have a chance to comment. Of course, we understand that goes for industry too.

Again, for the new guidance, we feel that if it's a device that is reviewed by CDRH and by CBER, as many of our products are, that they should issue those guidances jointly.

Here are some other priorities that we as a corporation would like to see. The 1991 MOUs are kind of old, and everybody agrees to that. We would like to see the task force that is supposed to be reviewing that MOU and what they have been doing. We think that any 1991 MOU revision would require the cooperation of all three of the major product review centers at FDA, not simply CDRH and CBER.

And, finally, that the new MOUs, if there are any, should really take harmonization into account. We have already heard from the people in the audience that harmonization is an issue. It's going to get a bigger issue as our global trade increases and as other countries become more sophisticated and more demanding in their understanding of what constitutes real product performance.

We have some other priorities. We would like to see, just to save us confusion, the same tracking systems

and publications for device submissions for both CDRH and CBER. We would like you to perhaps share databases, begin to publish a single database. It would save us time, trouble, and a certain amount of confusion. Again, we would like the same system for review communications, if possible.

And, finally, another item that has come up already from the audience: If you have got a product, you should really not have to do more than one submission for it, or more than one type of submission.

And then finally our suggestions for a few new joint guidance documents, and once again my emphasis is on joint. We would like to see these two groups working together as much as possible.

We would rather see, in lieu of an MOU, we would like to see a guidance on criteria for determining where to send your premarketing submission. Now, that may be unique to Becton Dickinson. I'm not speaking for the industry. We would like to see a prioritization of the criteria employed to determine where a product should be reviewed.

We would like to improve and revise the Recognition and Use of Consensus Standards, and we would like CBER to be far more involved in that. We would like to see some CBER-reviewed devices on those supplemental lists, and more methods standards for evaluation of product characteristics.

There are many international, highly regarded professional groups developing standards for the evaluation of product characteristics. Why isn't CBER more participative? Again, the other thing is nomenclature standards. We would also like to see common nomenclature.

And last but not least, of course we really appreciate the cooperation that has gone on so far, and we hope to see more of it, in the area of software evaluation and software development.

And finally, then, the ways that industry can help. Work with professional groups to coordinate guidance development. Once again, if CBER is more sensitive than CDRH in the area of allowing industry input at an early stage, how about working together with various professional groups, ISLH, for example, to coordinate guidance development. Suggestions for new guidances? Well, you have already gotten those.

Another area that I think is kind of not well developed is our customers, the health care practitioners. Those are the people that want the high quality products. We would like to see them inputting a little more into guidance development.

And of course my last message: Devices are a legal category, with legal requirements, regardless of the reviewing Center. And Memorandums of Understanding are far

more easily change than that basic fact of food and drug law.

And thank you for listening to me.

DR. DONLON: Thank you, Anna. We'll proceed with the other presentations and then have combined questions and answers after we are completed with the presentations.

Our next presenter is Nancy Hornbaker. She is the Director of Regulatory Affairs and Nucleic Acid Diagnostics for Bayer Corporation. Nancy?

MS. HORNBAKER: Thanks, Dr. Donlon. I am here today representing the Diagnostics Division of Bayer Corporation. Their diagnostics is headquartered in Tarrytown, New York--let's try this. How is that? Is that okay? More? How about that? Is that good? More, higher? Are we okay now?

Again, I am here today representing Bayer Corporation's Diagnostics Division, which is headquartered in Tarrytown, New York. Our Diagnostics Group manufactures --first of all, manufactures and markets products that serve the major sectors of the in vitro diagnostics industry, and that would include self-testing, point-of-care testing and laboratory testing. Our in vitro diagnostic products are regulated under the FD&C Act by both CDRH and CBER, which brings us here today.

The passage of FDAMA has clearly presented CBER

with additional challenges. The Center must support routine operations while devising and then implementing the systems and documentation and all their supporting efforts that support and meet the requirements of the act.

There are pressures to accelerate the submission review process, yet there are pressures that the Center should not compromise the safety of the Nation's blood supply or put the public health at increased risk. So resources are scarce--we have heard that earlier--but the tasks are many.

FDAMA has brought change to FDA, and I think we will all agree that managing change is one of the hardest things that we as individuals can do, let alone large organizations. So I would just like to say that we commend CBER on how it has handled these changing times and for the progress that the agency has made to date.

CBER has invited us here today to provide input regarding the kinds of medical device guidance documents that it should develop, finalize and implement using Good Guidance Practices. CBER has also asked for some priorities in addressing those guidance documents. First we will discuss a little bit some general recommendations relative to opportunities for CBER actions, and then a few comments on some specific guidance documents that we are interested in CBER addressing in the near future.

First of all, for some general guidance issues, we recommend that CBER, using Good Guidance Practices, formalize any of the de facto processes, procedures, recommendations, whatever, in formal guidances that have been out there for a while and are still in use.

By doing so, manufacturers will be informed, well in advance of any regulatory submission process, of CBER's expectations, and will be able to address those specific issues whether they pertain to a clinical study design, such as numbers of specimens or populations to be tested; whether it pertains to manufacturing issues or other topics.

As a result, we believe interactions between CBER and the manufacturers should be more productive, since both sides will understand in advance what CBER's expectations are. Also, we believe that regulatory submissions should be more complete, since again manufacturers will understand what CBER's issues are and will have had a chance to address them before the submission is made.

We believe that if the regulatory submissions are more complete, it would follow that the CBER review time should accelerate. And we have heard this earlier, but I think it's always a good time to remember that guidance documents are just that. They are guidances. They are not requirements, they are not rules, they are not binding.

But they do present at least one possible way of

meeting requirements. We strongly urge that CBER recognize that there may be alternative ways, and that these alternatives need to be carefully considered when they are presented by industry.

Secondly, we believe there is a greater need for cross-Center, that is specifically here CBER and CDRH, collaboration and harmonization in the following areas. When possible, the development of common guidance documents and processes/procedures to support those guidances. The common or cross-Center review of guidance documents and procedures. The development of common interpretations, once those guidance documents are vetted and finalized.

We believe cross-Center reviewer training would be appropriate, and cross-Center efforts at implementing common implementation schemes for the guidances and the supporting processes or procedures.

We also encourage CBER to accept earlier and greater utilization of our industry resources in the guidance document process. That would include setting priorities and possibly preparing initial drafts of guidance documents for CBER's further processing.

When appropriate, we believe it would be useful for industry or their trade groups to work with CBER to cosponsor workshops, sessions such as the one today, to develop the guidances, or probably a better use would be to

solicit feedback on guidances that have been published for comment. It would also be a useful forum to discuss the underlying bases for these guidance documents.

We think it is important to foster open communication and great cooperation between CBER and industry, and we think that these kinds of sessions will help ensure that industry comments are heard, understood and carefully considered. It would be a really good interactive process that we could both start to understand each other's wants and needs a little better.

We also recommend that CBER develop and implement tracking and routine communications systems that will give CBER and its stakeholders visibility regarding priorities and the status of guidance documents. When there are changes in priorities that would either accelerate the publication or finalization of a guidance or decelerate that process, that kind of system would give stakeholders a communication mechanism so that we will all be informed of what those priorities really are. But, of course, to be really effective any tracking system would have to have really frequent and routine updates.

Also, we believe that when CBER acknowledges its acceptance of a guidance document from CDRH or another agency, CBER should also acknowledge whether it adopts that guidance in full or in part. When it adopts a guidance in

part, we would like to see comments that would explain what parts are fully adopted, which parts are not, with some explanatory remarks about why CBER believes there are CBER-specific pieces of information that should or should not be included in that guidance.

In addition to developing guidance documents for industry, we suggest that CBER work jointly with CDRH, when it's appropriate, to develop guidance documents for itself, specifically for reviewers. And we believe that some key areas for those guidances would include the review criteria for 510(k)s, all kinds, traditional, abbreviated and special; and review criteria for PMAs, both traditional PMAs, modular PMAs, and special supplements.

Now for a few specific comments about some specific guidances we would like to see in the very near future. First there are some new ones.

We think there is a great need right now for a guidance document on agreement meetings, including how to and when to. For example, what information needs to be provided to CBER before an agreement meeting? When does it have to be provided? What is the most reasonable format for an agreement meeting? And how and when will the resulting agreement be documented and conveyed?

We think a second important guidance is an approach to CBER's implementation of FDAMA's "least

burdensome" requirements. Guidance is needed to define the framework for CBER's implementation of these "least burdensome" requirements, and we believe the guidance document would provide criteria for defining, first, defining scientifically valid information that would allow the agency to determine either SE or to determine safety and effectiveness with the least burden to industry.

We think that guidance would therefore start to stop what we sometimes see as regulatory requirements creep. For example, as more clinical utility information for a marker or analyte appears in literature, specifically medical literature, we often see changes in clinical practice based on that information, and just based on clinical experience.

When the utility of an analyte and its use in clinical practice is well known and well documented, we think the "least burdensome" guidance should place less emphasis on the demonstration of clinical utility of that marker. More emphasis should be placed on studies required to demonstrate that a particular device has the performance attributes necessary to measure or detect that analyte.

In other words, there would be less focus on what would be considered a more traditional sense of clinical utility and more focus on determination of analytical performance, such as reproducibility, sensitivity, a

particular device's ability to detect or measure diverse strains of an organism, and so forth.

We think there should be, and we heard today that it sounds like the agency is working on some guidance documents for NAT for Hepatitis C and B to be used in screening the blood supply.

We also recommend a couple of guidance documents revisions, and one is--perhaps "revision" is the wrong word in this case. A guidance document entitled "Guidance for Industry in the Manufacture and Clinical Evaluation of an In Vitro Test to Determine or Detect Nucleic Acid Sequences of Human Immunodeficiency Virus, Type 1," was drafted and sent for comments in mid-98, but that document has not been finalized yet. We recommend that that document be finalized relatively soon.

Also, we consider an old "Points to Consider" document from 1989, and that was the "Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus, Type 1," that needs to be updated. The guidance is still in effect, as far as I know, but the information in that guidance is outdated and sometimes now inappropriate.

In closing, we would like to comment on a positive note that CBER's intentions and progress encourage us. For example, CBER's initiative in pursuing the opportunity to

downclassify from Class III to Class II new IVD tests for HIV genotyping drug sensitivity or resistance assays is commendable. This effort demonstrates the agency's desire and the ability to minimize regulatory burdens. And we think the recent CBER HIMA Vendor Day is a good example of CBER's increased outreach and interactions between industry and CBER.

And we think you all have made a good start down a new and sometimes bumpy road. We think with CBER working with industry we can create a road map that will provide even more clarity and more direction and provide some specific milestones so that we know where we are and we can correct our course if we need to.

So we would like to thank you for the opportunity to suggest some additional areas for action, and say that we as a company look forward to continuing to work with CBER to improve our collective abilities to get high quality, safe and effective, important products to the marketplace.

DR. DONLON: Thank you very much, Nancy, for those very thoughtful comments.

Our next industry speaker will be Carolyn Jones. She is the Associate Vice President for Technology and Regulatory Affairs at the Health Industry Manufacturers Association, known as HIMA. Carolyn?

MS. JONES: Thank you. Good afternoon. I am here

representing the Health Industry Manufacturers Association. I think you have copies of my presentation, so I will skip the usual introductory information about HIMA and get straight to some of our comments.

Today CBER is faced with several challenges. Charged with implementing complex and demanding statutes, CBER wields enormous power that has significant economic impact over medical device manufacturers and their customers. Public expectations of CBER's ability to ensure the safety of the nation's blood supply by providing the most technologically advanced products, risk-free and immediately, are understandable but not always realistic.

As a result of the burden of its PDUFA responsibilities and current fiscal restraints, CBER lacks the needed staffing resources to meet its device responsibilities. Such challenges require optimal levels of communication, cooperation, consultation and collaboration.

Spurred by the passage of FDAMA, CBER has embraced these challenges with a new vision and a sense of enthusiasm and dedication. CBER has canvassed stakeholders and has listened seriously and thoughtfully to their concerns, and is moving to address those concerns. This is being accomplished through its Device Action Plan, interaction with the device industry--for example, the CBER Vendor Day--and its focus on the need to develop guidance documents to

enhance its device review processes.

HIMA is greatly encouraged by CBER's beginning efforts. We support the agency's ongoing efforts to seek improvements, and welcome the opportunity to provide suggestions for further improvements.

We are here today to discuss CBER's medical device related guidance documents development process, and to establish priorities for the development of guidance documents for these devices. As we have stated many times, any new project should begin with an evaluation. That evaluation should take into consideration the tools you already have and those that are needed to perform the task.

To develop and implement Good Guidance Practices, a good starting point for CBER is to first evaluate its current processes to determine what things add no value or little value to the guidance development process; stop all functions with no or little payoff; expand on those that work; and, with help from your stakeholders, look for new approaches to enhance the process. While CBER is not here today to ask for possible approaches to guidance document development, that is, Good Guidance Practices, to its credit, CBER is asking its stakeholders what its priorities should be.

Although long product review times remain the issue of primary concern, manufacturers also note an

apparent disconnect between what CBER wants in product submissions and what manufacturers think CBER wants in product submissions. After waiting six months to receive questions on a submission, on average it takes a manufacturer three to six months to respond to CBER's queries. CBER cites poor product submissions as the reason for the delay.

It's not reasonable to believe that most of industry gets it wrong the majority of the time. We believe that part of the problem is lack of clear guidance on submission requirements and a reluctance to embrace change. CBER and the industry must work together to develop guidance documents that clearly define what is expected of both parties.

Before I address priorities, I would like to suggest some process changes for CBER's consideration. We suggest the following items for CBER's consideration:

Discontinue the practice of developing guidance documents without industry input. In the past CBER drafted guidance documents and allowed industry to comment on the document. The comments may or may not be accepted. That process leaves most companies feeling that their input was not wanted or valued and that their expertise is questioned. Real input would mean that there would be a dialogue between CBER and industry, an exchange of ideas before a

document is developed.

We can't stress strong enough that we hope that CBER will look to industry for help. This doesn't mean that CBER needs to hold a stakeholder meeting every time it wants to develop a guidance document, but it does mean that guidance documents should not be developed and implemented in a vacuum.

A guidance document is only as good as the input provided to develop it. A guidance document with an inappropriate approach benefits neither CBER nor industry. It merely wastes time that could be spent on more productive pursuits. Work with industry to develop templates and guidance documents to make each type of submission--BLA, 510(k), and PMA--and review process simpler.

Another way of gaining industry input is for CBER to publish its guidance document "wish list," and I think we have seen some of that today. Industry could comment on that list and even offer to spearhead the development of specific guidance documents. I will speak more about the "wish list" concept later in my presentation.

Another suggestion is that CBER develop joint guidance documents with CDRH or adopt CDRH guidance documents where appropriate. Communications between CBER and CDRH have improved. We suggest that CBER take full advantage of the improved communications to work with CDRH

to develop joint guidance documents. Where necessary to address specific blood safety concerns, additional review requirements should be added to the consolidated guidance document.

In the spring, CBER published a list of CDRH guidance documents that it planned to adopt. In light of FDAMA, this was appropriate. It was appropriate that CBER adopt the device guidance documents. CBER has complied with the letter of the law.

The question is whether CBER is truly incorporating the spirit of the guidance documents into the review process. From an industry perspective, we do not believe so. The number of additional requirements makes CBER's adoption of many of the CDRH guidance documents of minimal or no value. In such cases it would have been less burdensome for the manufacturer not to follow the CDRH guidance.

To allow continued use of the guidance documents adopted by CBER, and to conserve both CBER and industry resources, CBER should clearly outline where additional requirements may be imposed; explain why the additional requirements are necessary; and vet the additional requirements with your customers, the blood banking community and the device industry.

We also ask that CBER provide some explanation of

the criteria used to determine which CDRH guidance documents would be accepted, so that industry can understand why certain documents were not adopted.

Another suggestion is to develop guidance documents for reviewers that harmonize CBER device review processes, particularly for instrumentation and software, with CDRH review processes, so that instrumentation/software that can be used for blood screening and for diagnosis would not require dual review. Harmonizing device reviews would streamline the process and facilitate getting these much-needed technologies to market.

We also suggest that CBER keep industry informed about changing requirements. Often when a manufacturer follows an available CBER guidance document, for example, specifying sample size for clinical studies, and they may even file an IND with the sample size clearly identified in the clinical protocol, upon submission the manufacturer will be told that more test specimens are needed.

If guidance documents are to be considered the current thinking of the agency, they must be updated when the agency's thinking changes. Guidance documents should represent a consensus within the agency and its stakeholders, not the opinion of a single reviewer.

Considering the length of time it takes to issue a new or revised guidance document, some thought should be

given about how much information could be disseminated before issuance of a revised or updated guidance document. I think use of a web site or some other public meetings or something of that nature would be instrumental in providing CBER the opportunity to let industry know when their thinking on a certain guidance has changed, if there is not ample time to put out a revised guidance.

Use of national and international standards, where appropriate, would also improve the process. As time and resources shrink, CBER should look for opportunities not to reinvent the wheel. FDAMA provides for the adoption of standards. Many scientific experts, including FDA's own, are substantially involved in developing standards for medical devices, or portions thereof, as part of national and international consensus committees.

Scientific issues associated with such standards are debated and discussed in an atmosphere not governed by a single company's product, government entity, or academic institution. Such standards, and industry's declaration of conformance thereto, are effective surrogates for FDA's independent scientific review.

We recommend, therefore, that both industry and CBER increase their participation in standard-setting organizations, and that CBER recognize such standards and defer to them in the application process. If there is a

standards that addresses CBER's needs, do not waste time developing guidance. Cite the standard.

And we recognize that there are not many or any standards at present that can be applied, but we ask CBER to get involved in the standards development process so that this can be a way to sort of offset some of their necessity for them to develop guidance on their own.

Remember that guidance is not binding. CBER has often applied guidance documents as though they were regulations. Guidance is not binding. They are static documents. They capture the thinking of the moment, and they should not be held out as the only way to obtain valid scientific data, a thought very well stated in your own disclaimer. If a manufacturer has chosen another method to obtain valid scientific data, CBER should welcome, not discount, alternatives that have a sound scientific basis and that may have a potential for accelerating the review process.

As for guidance priorities, on several occasions CBER has asked the device industry to supply its guidance document "wish list," and today I have a list of guidances that have been considered by industry. Some of the documents on our list are not new. They are documents that are currently being implemented in draft form, or CBER documents that need major revision. But I will first

address the new guidances.

Nancy sort of alluded to it in her presentation, but I guess we are looking at it from a little broader perspective. We think there is guidance needed for industry on presubmission meetings. The document would establish a framework for presubmission meetings with industry, define the basic elements of a successful pre-meeting data package and how the agreement will be documented.

We also recommend guidance on Automated Apheresis Devices used as Ancillary Products in the Production of Stem Cells. The document would outline the submission requirements for apheresis devices used in the production of peripheral blood hematopoietic stem cells intended for transplantation or further manufacture.

CBER's application of FDAMA's "least burdensome" provisions is an area ripe for a guidance document. Device manufacturers need to know how CBER plans to implement FDAMA's "least burdensome" provisions.

CBER's application of CDRH's 510(k) paradigm. I think some explanation needs to be given of how CBER plans to apply those paradigms.

Guidance on establishing criteria for selection of sample populations to support device performance characteristics. The document would provide industry with a clearer understanding of CBER processes, and would provide a

statistical rationale for the selection of sample size.

NAT for Hepatitis tests used in blood screening. Again, we were happy to see that was on CBER's list as well.

As for current guidances, these are guidances that CBER already has out, they either need to be revised or finalized, and I will just run through the list fairly quickly.

Recommendations for Collecting Red Cells by Automated Apheresis Methods; Guideline for the Validation of Blood Establishment Computer Software; Guidance for the Manufacture and Clinical Evaluation of IVD Tests to Detect Hepatitis Markers; Points to consider in the Manufacture and Clinical Evaluation of In Vitro Diagnostic Test to Detect Antibodies to the Human Immunodeficiency Virus, Type 1; Revised Recommended Methods for Evaluating Potency, Specificity, and Reactivity of Anti-Human Globulin; Revised Recommended Methods for Blood Grouping Reagent Evaluation; Guidance for Industry in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Virus.

Change Notification Guidance. This was one that came up sort of late in our discussions with our industry participants. They said more examples were needed of non-facility changes, such as in process release testing, lot release panel composition, and manufacturing process

changes, are needed for addition to the 21 CFR 601.2 and to CBER's guidance document.

These items are not listed in any priority, and cover IVDs, blood bank software and blood processing devices. I would like to express HIMA's willingness to work with CBER to develop a process and ultimately guidance documents that will allow CBER and industry to bring safe and effective medical devices to market in a timely fashion.

In closing, HIMA thanks FDA for the opportunity to provide these suggestions. We look forward to working with CBER as a partner in this effort to continue to improve its review and inspection processes. Thank you for the opportunity to present these comments.

And just one thing before I go on or close. One of the guidance documents that we listed under new guidance, we do have a working group at HIMA that is drafting a document for CBER's use and consideration. We recognize that there are resource constraints and time constraints on CBER staff, and we have asked our industry to step to the plate to assist CBER in developing some of these guidance documents, and I know that other trade associations out there will do the same.

Thank you.

DR. DONLON: Thank you, Carolyn, for those excellent comments.

Before we proceed directly to the questions and answers, I just want to make a general invitation, if there is anyone in the audience who wants to make a public statement for the record. I would also remind you that there is a 60-day comment period for the docket, so if you are not prepared to make a public statement here and now, today, you are certainly welcome to reason out that statement and submit it to the docket within the next 60 days.

[No response.]

DR. DONLON: Okay. Let's proceed. We have about 15 minutes for questions and answers before the plug is pulled on our communication systems here. Are there any questions from the audience, members of the audience here?

[No response.]

DR. DONLON: Okay. Let me--I have two questions on faxes but I'm not sure how the panel will handle these, since one of them is directed to CBER.

MS. JONES: You should answer it.

DR. DONLON: Yes. It says, "Can CBER comment on the following: Number one, development of guidelines for a comment period for guidances." A guideline for a comment period for guidances.

I believe that guidances, as Peggy Dotzel has indicated in the presentation earlier this afternoon, where

a Level 1 or Level 2 guidance is published in the Federal Register, there is a comment period. A Level 1 guidance basically allows for comments prior to being finalized and implemented. The Level 2 guidances, even though they are published at the time they are implemented, still have a comment period available to them.

So either way, guidances published under the guise of the Good Guidance Practices have comment periods associated with them, and those periods would be adhered to. I think in general they are 60 days. Is that correct, Steve, roughly?

MR. FALTER: Sixty to 90 days.

DR. DONLON: Sixty or 90 days, comment periods on guidances that are published.

The second part of that question is, I guess, a request for posting all comments on guidances on the web page. Again, my sense is that relative to the Level 1 guidances, as the final guidance is published, there is a comment to those guidances, but for the Level 2 guidances, comments received on that, since they are already finalized, they are not necessarily published. But it is something we will certainly take into consideration.

Any comments or questions from the audience at this point?

[No response.]

DR. DONLON: Okay. This is a question directed at Carolyn Jones or Kathy Zoon, and I would add Richard Lewis as well. Pay attention, Richard. It's a long question.

"Why is it necessary for blood component collection facilities to duplicate submissions for which equipment manufacturers have already received clearance from CBER? Validation of equipment performance is an example. Why can't equipment manufacturers provide certification that blood bank personnel have been trained to properly operate the equipment and can obtain the results that were submitted in the manufacturer's submission?"

Do you have an idea, Carolyn?

MS. JONES: I think that manufacturers do validate their devices, and that should not--the user should not have to make that additional submission. I would sort of agree with the questioner, but I'm not sure whether a certification from the manufacturer that the user has been trained would necessarily meet CBER's needs, and I think you guys would need to respond to that.

I don't think that the user should be required to make a new submission, but some other mechanism should be in place to assure CBER that the device has been properly placed in the facility and that the folks have been trained, but in the form of a submission, I think that's unnecessary duplication of effort.

DR. DONLON: Okay. Richard, can you give us our experience in that area?

DR. LEWIS: I would agree that we look at the particular facility submission from a different perspective than a manufacturer would who is implementing a device in a facility, so that the validation of a particular technology in the establishment is different than validating that the particular device can function and function properly, that it makes a safe and effective product. It's a second layer of evaluation.

DR. DONLON: Okay. Thank you.

The last part of that question was, "Are these areas appropriate for guidance documents?" And I would answer yes. Basically any area of which there is--it is unclear or possibly confusing to industry or the public is an area that we certainly may appropriately use guidance documents.

Any questions from our audience here?

MS. JONES: I have a question from the panel.

DR. DONLON: Very good.

MS. JONES: One of the things that I have begun to appreciate in my interaction with the Center for Devices is that once a guidance document has been drafted, it is placed on the web site even before the document is actually announced in the Federal Register, and it gives the industry

an opportunity, a much longer opportunity to take a look at the guidance document and develop comments to it.

So I am wondering, you know, the earlier question regarding the need for guidance that outlines how much time is given to comment on a document, such a guidance wouldn't be needed if, once the guidance is drafted, it's placed on the CBER web site, and the actual comment period were defined in the Federal Register, because I know there is a lag time between the development of the guidance document and the actual drafting of it, before it actually goes on--goes into the Federal Register. I was wondering about the possibility of that also occurring at CBER.

DR. DONLON: Steve Falter is walking to the microphone to answer that question.

MR. FALTER: I'll try, at least. In some cases we do do that. Our position, though, is that a guidance document is not a CBER tool, it's an agency tool. When it's published, it's signed out at the Commissioner level, and because of some of the areas we're dealing with which are somewhat controversial and deal with issues of considerable interest, until the blessing from the highest levels have come on the guidance document itself, we do not release it even though CBER is fully supportive of it.

That leaves a very small window between the time when the final blessing is bestowed on the guidance and the

time that it publishes, a few days. And I do think we could save a couple of days in that way, and we'll take that under consideration, but the change would not be drastic in most cases.

MS. JONES: So you're saying that your time from actual drafting to getting in the Federal Register is actually much better than CDRH's lag time. Yours is a couple of days, so it really wouldn't add that much.

MR. FALTER: No, no. The time between where the last person at FDA has approved the guidance and notice of availability, to where it publishes, is small. I'm sure we have about the same track record as far as agency review.

MS. LONGWELL: Are you saying that there are more elaborate review procedures for guidances generated by CBER than for guidances generated by CDRH?

MR. FALTER: I don't think the policy was developed in relation to other Centers. It's just the problems we had where there are last minute changes, differences as to what is actually issued, that occur in the upper agency or even departmental level, and therefore we don't consider the guidance document as representing an agency position until the last manager has seen it. I really don't know what the other Center's experience is on that. That is our policy.

DR. DONLON: Okay. Other questions from the

audience?

[No response.]

DR. DONLON: Then let me try to briefly sum up this afternoon's program. Clearly guidances are not regulations and are not binding, as Peggy Dotzel reminded us. However, I think guidances clearly can facilitate submissions, submission reviews, and dialogues with industry. I think that has been clear from the discussions we have had. And therefore they benefit, I think, both industry and agency staff. I think they are mutually beneficial.

I think, however, we have to remember that the CBER staff who develop guidances in a specific area are the same staff who are doing the reviews of the submissions, and as yet we have only been able to have people do one thing at a time in their jobs, although we recognize the advantage of guidances in facilitating submissions.

I think the suggestions today from industry and the questions that we had from our off sites were very helpful in directing us to priorities for guidances now and in the future. We certainly intend to review the transcript of this meeting as well as the comments that come into the docket over the next 60 days, and we will discuss them actively internally and help us develop our own priorities as far as guidance documents and interactions with industry

in developing those documents will go.

Again, I wish to thank Gail Sherman of our Office of Communications, who facilitated this workshop, as well as her able assistant, Melanie Whalen, who paid attention to the details and was able to get us connected to Boston, Denver, Los Angeles, and Alameda.

Thank you very much, all, for your presentations. I think it has been very helpful to us and has been very productive.

[Whereupon, at 3:58 p.m., the workshop was concluded.]